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Factors associated with hospitalisation and mortality of people with Parkinson's Disease: Analysis of a large UK primary care database.

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Declaration

I, Olaitan Christiana Okunoye confirm that the work presented in this thesis is my work. I also confirm that I have indicated in my thesis where information has been derived from other sources.

Signed: 

Abstract

Background: Parkinson's disease (PD) is characterised by worsening motor symptoms, falls/fractures and infections with disease progression, leading to hospitalisation and in some instances, death. Quality data on hospitalisation and mortality in PD is lacking.

Objective: To investigate hospitalisation, mortality and incidence of PD over time in UK primary care setting.

Methods: Through a systematic review and meta-analysis, estimates of the pooled prevalence of common reasons for hospitalisation was calculated. Three cohort studies using data from The Health Improvement Network (THIN) were conducted in the period 2006-2016: [1] Incidence of PD; [2] Mortality and [3] Hospitalisation in PD.

Findings: In the review, from the nine included eligible studies, the main reasons for hospitalisation and their pooled prevalence among PwPD were infections (22%,95%CI:16%-30%), worsening motor features(19%,95%CI:13%-27%), falls/fractures(18%,95%CI:14%to21%), cardiovascular comorbidities (13%,95%CI:9%-18%), neuropsychiatric (8%,95%CI:4%-13%) and gastrointestinal complications(7%,95%CI:4%-11%). In my empirical studies, the incidence of recorded PD gradually decreased using the stricter case definitions but remained stable using the broadest case definition over time. For the strictest case definition (diagnostic Read code and at least two prescriptions of antiparkinsonian medication), the incidence of PD was 60.42 in 2006 and dropped to 42.24 cases per 100,000 person years at risk (PYAR) in 2016 and for the broadest case definition (diagnosis Read code or symptom Read code

or at least one prescription of antiparkinsonian medication), the incidence of PD was 149.20 cases in 2006 and this reduced slightly to 143.70 cases per 100,000 PYAR in 2016. 10,104 incident PD cases were identified and matched with 55,664 people without PD. Overall, rates of hospitalisation (IRR:1.33, 95%CI:1.29-1.37) and mortality (IRR:1.14, 95%CI:1.09-1.20) were higher in PwPD than those without. Hospitalisation rates were higher among people with PD (PwPD) in the younger age-group than those without PD in the same age-group. Other sociodemographic factors had no impact on hospitalisation and mortality in PD. PwPD were more often admitted with falls/fractures, infections, gastrointestinal complications, dementia, psychosis/hallucinations, postural hypotension, electrolyte disturbances, stroke, and surgical procedures compared to those without PD. Further results showed a widening mortality gap between PwPD and the general population.

Conclusions: PD is associated with increased hospitalisation and mortality. The complications of motor and non-motor features of PD are amongst the main reasons for admission, some of which could be managed pro-actively to avoid admissions and maybe prevent death. Future studies should be directed at exploring effectiveness of preventive strategies to reduce hospitalisations and maybe mortality among PwPD.

Impact Statement

Parkinson's disease (PD) is a slowly progressive but the fastest growing neurodegenerative disorder of our time. It is characterised by many motor and non-motor features which can result in serious and potentially life-threatening outcomes such as hospitalisation and mortality, particularly in advanced disease.

Work from my PhD provided insight into the rates of hospitalisation and mortality of people with PD in the UK. Through a systematic review and meta-analysis, I identified top reasons for admission which included falls/fractures, worsening motor symptoms of PD, infections, cardiovascular disease, gastrointestinal and neuropsychiatric complications. Some of these complications have been reported in literature as major causes of death in PD. Early identification and treatment of some of these reasons by clinicians (particularly the modifiable ones) may lead to reduction in unplanned admissions and likely death resulting in a better quality of life for patients and reduce cost of healthcare service. In addition, data from this study provides a benchmark for clinicians, researchers, and policy makers against which interventions to prevent hospital admissions can be developed and quantified This review has been published in Parkinsonism and Related disorders and has had an impact on PD related research with 18 citations in over 12 months.

Furthermore, my use of primary care electronic medical records to identify people diagnosed with PD in the UK demonstrated that the source of data could be used to investigate incidence of PD using four case definitions. Given that there are variations in previous reports on PD Incidence which are

attributed to differences in healthcare systems, coding practices and case ascertainment, these four case definitions could be improved, validated and incorporated into current primary care patient management software to increase notification of PD cases and improve timeliness of care. This study provides robust data on incidence of PD diagnosis in the UK and also gives baseline case definitions for future research. A poster of this work was presented at the World Congress of Neurologists in Dubai (2019) and at the American Academy of Neurology Virtual meeting (2020).

Another study from this PhD also identified that mortality rates of people with PD and controls slowly declined from 2007 to 2016. Mortality rates in those without PD outpaced those with PD declining at a faster rate leading to a widening mortality gap between people with PD and matched controls implying that current available interventions to reduce mortality in the general population has not impacted people with PD. Therefore, the need for further research on interventions that can detect/treat early signs of complications, potentially reducing mortality. Also, annual reviews of some of falls and swallowing problems (which common causes of death in PwPD) should be included in PD care. This study has been published in Movement Disorders Journal.

Finally, my research on hospitalisation which is the first and largest study of its kind in the UK, provides data on the rate and potential causes associated with admissions in patients with PD. These data can be used to develop evidence based preventative measures targeted at specific complications of PD in order to reduce hospital admissions resulting in improved quality of life for PD patients, reduced costs on patients, caregivers, healthcare system and society.

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Disseminated work from thesis

Two manuscripts have been published based on study conducted in this thesis. This is based on the study presented in Chapter 2. These are cited below:

- Factors associated with hospitalisation among people with Parkinson's disease – A systematic review and meta-analysis. Parkinsonism Relat Disord. 2020 Feb; 71:66-72.
- Mortality of people with Parkinson's disease in a large UK-based cohort study. Time trends and relationship to disease duration (published online on August 5th, 2021 in Movement Disorders Journal)

Two other manuscripts based on studies presented in Chapters 4 and 6 have been submitted for publication.

I have also presented my work at 2 international conferences.

Poster presentations:

2019 World Congress of Neurology Dubai:

Trends in the Incidence of Parkinson's disease diagnosis between 2006 and 2016: Analysis of a large UK Primary care database.

2020 American Academy of Neurology conference (Virtual conference):

Trends in the Incidence of Parkinson's disease diagnosis between 2006 and 2016: Analysis of a large UK Primary care database.

Abbreviations

ACU	Acceptable computer usage
AHD	Additional Health Records
AIC	Akaike's Information Criterion
AMR	Acceptable mortality recording
BIC	Bayesian Information Criterion
BNF	British National Formulary
CCRT	Cochrane Central Register of Controlled Trials
CDRS	Cochrane Database of Systematic Reviews
COMT	Catechol-*O*-methyl transference inhibitors
CPRD	Clinical Practice Research Datalink
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DARE	Database of Abstracts of Reviews of Effects
DBS	Deep Brain Stimulation
DVT	Deep vein thrombosis
GIT	Gastrointestinal
GP	General Practitioner(s)
GPRD	General Practice Research Database
HEED	National health service Health Economic Evaluation Database
HTA	Health Technology Assessment
5-HT	5-hydroxytryptamine/serotonin
IMS	Integrated Medical statistics
IRR	Incidence Rate Ratio
LB	Lewy body(ies)
L-DOPA	Levo-dopa
MAO-B	Monoamine oxidase B inhibitors
MESH	Medical subject headings
NOS	Newcastle-Ottawa scale
NMDA	*N*-methyl-D-aspartate-type
ONS	Office for National Statistics
PD	Parkinson's disease
PwPD	People with Parkinson's disease
PVI	Postcode variable indicator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PYAR	Person Years At Risk
RECORD	Reporting of studies Conducted using Observational Routinely collected Data
SCIE	Science Citation Index Expanded
SNpc	Substantia nigra pars compacta
STN	Subthalamic nucleus
STROBE	STrengthening the Reporting of Observational studies in Epidemiology
THIN	The Health Improvement Network
UCL	University College London
UK	United Kingdom
UTI	Urinary tract infection

Chapter 1 Parkinson's disease (PD): Overview

1.1 Chapter overview

In this chapter, I present an overview of Parkinson's disease including a summary of the literature on mortality and hospitalisation. I also present a summary of mortality and hospitalisation among people with PD and describe the specific aims and objectives of my research in this thesis.

1.2 Overview of Parkinson's disease

1.2.1 Background

Parkinson's disease (PD) is the most common neurodegenerative disorder of movement (de Rijk MC et al., 1997). Although it was first described in great detail by James Parkinson in a seminal essay on "the shaking palsy" more than two centuries ago, the conceptualization of PD has continued to evolve (Kalia LV and Lang AE, 2015). The cause of the disease remains unknown in most people with PD but in about 5% to 10%, genetic causes have been identified (Balestrino R and Schapira AHV, 2019).

The characteristic motor features are tremor, rigidity, akinesia/bradykinesia and postural instability. In addition to these motor features, many non-motor symptoms such as hyposmia, depression, disorders of sleep, cognitive impairment and autonomic dysfunction add to the overall burden of the disease (Khoo TK et al., 2013, Poewe W et al., 2017). Although specific investigations can help differentiate PD from other forms of parkinsonism, diagnosis of the disease is largely clinical. Loss of dopaminergic neurons in the substantia nigra

pars compacta (SNpc) and accumulation of misfolded alpha-synuclein found in intra-cytoplasmic inclusions known as Lewy bodies (LBs) are the pathological hallmarks of PD (Balestrino R and Schapira AHV, 2019). The resultant effect of this is significant death of dopaminergic neurons in the substantia nigra pars compacta leading to deficiency of dopamine within the basal ganglia, and neurodegeneration in other neuroanatomical areas (Gibb WR and Lees AJ, 1988, Kalia LV and Lang AE, 2015).

Pharmacological treatment (L-DOPA treatment) involving dopamine replacement remains the mainstay of treatment in PD, although alternative measures such as deep brain stimulation are used in suitable people. These treatment strategies only provide some symptomatic control allowing the patient sustained quality of life years after disease onset, but none are curative (Poewe W et al., 2017). With disease progression (PD being a progressive disease), severe disability develops particularly with treatment-resistant motor symptoms and non-motor features. Additionally, complications of long-term dopaminergic drugs and an array of other complications also occur which may lead to hospitalisation and death.

1.2.2 Epidemiology and risk factors for Parkinson's disease

Parkinson's disease (PD) is a disorder that occurs all over the world. It is the second most common neurodegenerative disease affecting both genders but with some predilection for the male sex (de Rijk MC et al., 2000, Baldereschi M et al., 2000, Van Den Eeden SK et al., 2003). Meta-analyses have estimated overall incidence of PD to range from 12-15 (Hirtz et al., 2007) and 16-19 (Twelves D et al., 2003) new cases per 100,000 individuals per year in the US and Europe respectively. A review has also reported estimates of overall incidence rates of PD to range from 1.5-22 per 100,000 person-years (Wirdefeldt K et al, 2011). The reason for this wide variation is probably due to differences in demographic characteristics of the study population or study design.

Parkinson's disease is uncommon in people who are 50 years and below. However, in those 60 to 90 years of age, incidence of PD increases 5 to 10-fold (Twelves D et al., 2003, Van Den Eeden SK et al., 2003, Savica R et al., 2013). The overall prevalence of PD in developed countries is estimated to be 0.3%, 1% in people 60 years and older and 3% in people 80 years and older (Pringsheim T et al., 2014, Lee A and Gilbert RM, 2016). The estimated prevalence and incidence rates of PD in Europe ranges from 25 to 12,500 per 100,000 and 5 to 346 per 100,000 person-years respectively (von Campenhausen S et al., 2005).

There appears to be racial, ethnic and environmental differences in the incidence of PD. Although systematic race-specific incidence studies have not been conducted in other multiracial populations, PD might be less common in Africans, African Americans and Asians. The explanation for this could be

geographic variation, variability of screening methods for case ascertainment and differences in survival rates (Van Den Eeden SK et al., 2003, de Lau LM and Breteler MM, 2006).

The major risk factor for the development of PD is age with prevalence and incidence rising with age and peaking after 80 years of age (Driver JA et al., 2009, Pringsheim T et al., 2014). This direction of growth has public health consequences; as a result of the aging population and the global rise in life expectancy, the number of people with PD is predicted to more than double by 2030 leading to increasing global burden of the disease (Dorsey ER et al., 2007). Being male moderately increases the risk of developing PD. In most populations, men are twice as likely to have PD compared to women (Baldereschi M et al., 2000, Van Den Eeden SK et al., 2003). Though a few exceptions to this exist in some populations for example one study conducted among the Japanese showed no difference (Kusumi M et al., 1996).

There are reports of several environmental risk factors linked to the risk of developing PD. In a meta-analysis, of the thirty potential risk factors examined, eleven were reported to be significantly associated with the risk of PD. Pesticide exposure, previous head injury, rural living, use of a beta-blocker, agricultural occupation and well-water drinking were reported to increase the risk of developing PD (Noyce AJ et al., 2012). On the other hand, tobacco smoking, coffee drinking, use of medications such as non-steroidal anti-inflammatory drug and calcium channel blocker; and alcohol consumption were reported to reduce the risk of developing PD (Noyce AJ et al., 2012). Furthermore, substances such as 1-methyl-4-phenyl tetrahydropyridine (MPTP) (Langston JW et al., 1983) and annonacin are reported to cause death of

nigrostriatal cells leading to a form of atypical parkinsonism (Angibaud G et al., 2004, Hoglinger GU et al., 2005). In addition, exposure to unsafe levels of certain substances such as manganese, trichloroethylene and carbon monoxide can cause some forms of parkinsonism with different clinical and pathologic features when compared to PD (Mittal S et al., 2017).

Family history is a risk factor for developing PD. A previous study showed that first-degree relatives of people with PD were two to three times more likely to develop PD when compared to controls. This paved way for more search for genetic causes of PD (Gasser T, 1998). Five to fifteen percent of people with PD are reported to have the familial form of the disease. The major genes associated with the development of PD are summarized in **Table 1-1.**

Table 1-1. Summary of genes associated with Parkinson's disease (PD) (Balestrino R and Schapira AHV, 2019).

Gene	Locus name	Protein name	Chromosome	Inheritance	Clinics	Frequency of PD	Protein function
SNCA	PARK1/4	Alpha-synuclein	4q21-23	autosomal dominant	EOPD	<1%	Synaptic
PRKN	PARK2	Parkin	6q25-27	autosomal recessive	EOPD, slow progression + dystonia	1% -5% (up to 44% in EOPD)	Ubiquitin-Ligase
UCHL1	PARK5	UCHL-1	4p14	autosomal dominant	EOPD, LOPD	<1%	Uncertain
PINK1	PARK6	Pten-induced putative kinase I	1p35-37	autosomal recessive	EOPD, slow progression	2%-5%	Mitochondrial kinase
DJ-1	PARK7	Protein DJ-1	1p36	autosomal recessive	EOPD, slow progression	1%	Cellular sensor of oxidative stress
LRRK2	PARK8	Leucine-rich repeat serine/threonine-protein kinase 2	12p11-q13	autosomal dominant	LOPD, slow progression	1%-5% (up to 40% in North African Berber Arab patients)	Multiple functions domain dependent
ATP13A2	PARK9	ATPase type 13A2	1p36	autosomal recessive	Atypical parkinsonism, Kufor Rakeb syndrome	<1%	Lysosomal protein
PLA2G6	PARK14	A2 phospholipase	22q13	autosomal recessive	EOPD, dystonia-parkinsonism	<1%	Unknown
FOXB7	PARK15	F-box protein 7	22q12-13	autosomal recessive	EOPD, atypical-parkinsonism	<1%	Unknown
VPS35	PARK17	Vacuolar protein sorting-associated protein 35	16q11	autosomal dominant or risk	Late onset Parkinson's disease	<1%	Unknown
GBA Earlier onset +	dementia	5%-25% (10%-30% in Ashkenazi Jewish patients)	Lysosomal protein		Glucocerebrosidase	1q21	Risk factor

1.2.3 Pathophysiology of Parkinson's disease

The loss of dopaminergic neurons which is followed by depigmentation of the substantia nigra pars compacta and the presence of Lewy bodies are the major pathological features of PD. Lewy bodies are round, intraneural eosinophilic inclusions which have a hyaline core and a pale peripheral halo which are composed of about ninety proteins and more (Wakabayashi K et al., 2013). The main protein constituents are alpha-synuclein and ubiquitin (Spillantini MG et al., 1997). Alpha-synuclein which is one of the main pathologic proteins has the tendency to misfold and subsequently become insoluble forming aggregates of beta-sheet-rich amyloid which accumulate and develop into intracellular inclusion bodies. During the aggregation processes, multiple toxic intermediates which are oligomeric and proto-fibrillar forms of the protein are generated. These impair several cellular organelles and processes including damage to the mitochondria (Hsu LJ et al., 2000), biological membranes (Danzer KM et al., 2007) and the cytoskeleton (Alim MA et al., 2004); impairment of lysosomal and proteasomal (Snyder H et al., 2003) and synaptic function (Scott DA et al., 2010) leading to neuronal degeneration. Approximately sixty percent of dopaminergic neurons are estimated to be lost at the time an individual is diagnosed with PD (Marsden CD, 1990).

The spread of alpha-synuclein through neurons tends to be in a prion-like manner resulting in a mechanism of transmission which is probably the explanation for the development of the pathological abnormalities described above (Brundin P et al., 2016). This mode of spread has led to a proposed model of Lewy body formation and alpha-synuclein deposition starting from the

dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, with further conveyance to the brain stem. Thereafter, at the late stages, there is further spread to the meso cortex and allocortex and lastly to the neocortex (Braak H et al., 2003).

There are reports of other models of alpha-synuclein spread suggesting that alpha-synuclein aggregation may start in the autonomic plexi of the gut and the spread ventrally (Klingelhoefer L and Reichmann H, 2015). There are suggestions that the gut microbiome may enhance this spread (Sampson TR et al., 2016).

1.2.4 Clinical features of Parkinson's disease

The clinical features of PD constitute characteristic motor features and a wide range of non-motor symptoms. The classical motor features of PD include bradykinesia/akinesia, rest tremor, rigidity (the three symptoms usually asymmetric) and postural instability (Gibb WR and Lees AJ, 1988). Others include gait abnormalities, freezing, postural disturbances such as Pisa syndrome (a tendency to lean to one side with lateral bending of the trunk which is reversible) and camptocormia (bending forward of the thoracolumbar spine more than 45 degrees) (Barone P et al., 2016), micrographia (continuous reduction in size while writing) (Wagle Shukla A et al., 2012), speech problems, abnormal eye movements and hypomimia (reduced facial expression) (Balestrino R and Schapira AHV, 2019) **(Table 1-2).** These features vary in manifestation to some extent in different people with the disease but, the classical motor features (tremor, rigidity, bradykinesia and postural instability) and response to dopaminergic therapy are required to fulfil the diagnostic

criteria of PD (Berardelli A et al., 2013). An important and diagnostic feature of PD is the responsiveness of these motor features to treatment with levodopa (Balestrino R and Schapira AHV, 2019) **(Table1-3).**

The heterogenous nature of clinical features between individuals with PD has led to the characterisation of different motor subtypes of the disease which include “tremor dominant”, “postural instability and gait difficulty” (PIGD) or “indeterminate” (Jankovic J et al., 1990, Stebbins GT et al., 2013).

Table 1-2. Motor and Non-motor features of Parkinson’s disease (Balestrino R and Schapira AHV, 2019).

Motor symptoms	Non-motor symptoms
Tremor	Hyposmia
Rigidity	Psychiatric symptoms: depression, anxiety, apathy hallucination, psychosis
Bradykinesia/akinesia/hypokinesia	Dementia/cognitive impairment
Postural instability	Sensory symptoms
Postural abnormalities	Genitourinary symptoms: urinary frequency, urgency, reduced libido, sexual dysfunction
Gait disturbances (freezing of gait, festination, start/target/ obstacle hesitation)	Gastrointestinal symptoms: constipation, delayed/reduced stomach emptying
Alterations in blinking/eye movements	Dysphagia, sialorrhea, dysarthria, hypophonia
Hypomimia	Disturbances of sleep and wakefulness
Micrographia	Cardiovascular symptoms: Blood pressure variations (postural, postprandial), dysrhythmias

Table 1-3. New diagnostic criteria for Parkinson's disease (Postuma RB et al., 2015)

Movement Disorders Society clinical diagnostic criteria for Parkinson's disease	
Diagnosis of clinically established Parkinson's disease	
1)	Absence of absolute exclusion criteria
2)	At least two supportive criteria and
3)	No red flags
Diagnosis of clinically probable Parkinson's disease	
1)	Absence of absolute exclusion criteria
2)	Presence of red flags counterbalanced by supportive criteria
If no red flag is present, there must also be at least 1 supportive criterion	
If two red flags, at least 2 supportive criteria are needed	
No more than two red flags are allowed for this category	
Supportive criteria	
1)	Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patients returned to normal or near-normal level of function. In the absence of clear documentation of initial response, a dramatic response can be classified as:
	a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment) or subjectively (clearly documented history of marked changes from a reliable patient or caregiver).
	b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
2)	Presence of levodopa-induced dyskinesia
3)	Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
4)	The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy.
Absolute exclusion criteria	
1)	Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia or cerebellar oculomotor abnormalities
2)	Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3)	Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphsia, defined according to consensus criteria within the first 5 year of disease.
4)	Parkinsonian features restricted to the lower limbs for more than 3 years
5)	Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6)	Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7)	Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
8)	Normal functional neuroimaging of the presynaptic dopaminergic system
9)	Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, feels that an alternative syndrome is more likely than Parkinson's disease.
Red flags	
1)	Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset
2)	A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment
3)	Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, nasogastric tube or gastrostomy feeding) within first 5 years
4)	Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5)	Severe autonomic failure in the first 5 years of disease. This can include orthostatic hypotension or severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction.
6)	Recurrent (>1/year) falls because of impaired balance within 3 years of onset.
7)	Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years.
8)	Absence of any of the common non-motor features of disease despite 5 years' disease duration. These include sleep dysfunction (sleep-maintainance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia or psychiatric dysfunction (depression, anxiety or hallucinations).
9)	Otherwise, unexplained pyramidal tract sigh=ns, defined as pyramidal weakness or clear pathological hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
10)	Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.

This characterisation is important because of the distinction between the subtypes with regards to aetiological factors, disease severity and progression and response to treatment. There are reports that people with PD with “postural instability gait difficulty” form tend to experience a severe and rapid disease progression compared to the “tremor dominant” form (Fereshtehnejad SM and Postuma RB, 2017).

Non-motor features of PD are usually not reported until the individual is asked about them. They include swallowing difficulties, sialorrhea, sleep disorders, pain, autonomic, gastrointestinal, neuropsychiatric and cognitive problems. Although under-investigated by physicians, most people with PD report non-motor features if adequately assessed. These symptoms worsen with disease progression resulting in reduced life expectancy and poor quality of life. In addition, non-motor features are a major cause of disability in people with PD (Martinez-Martin P, 2014, Schapira AHV et al., 2017, Balestrino R and Martinez-Martin P, 2017) which may lead to hospitalisation and subsequent mortality.

1.2.5 Treatment of Parkinson’s disease

There were currently no disease modifying treatments for PD at the time of this review. Treatment of PD is predominantly pharmacological with the aim of achieving symptomatic control through the dopaminergic pathway (Balestrino R and Schapira AHV, 2019). However, in advanced PD, Deep Brain Stimulation (DBS) is a treatment option which is being used.

1.2.5.1 The main antiparkinsonian medications include:

- **Levodopa:** This is the most effective antiparkinsonian medication used for the treatment of motor features of PD. It is reported to be the gold standard for the treatment of PD (Fox SH et al., 2011). Levodopa which is usually given in tablet form (many times a day) or duodenal infusion in advanced disease crosses the blood-brain barrier and gets converted to dopamine in the residual dopaminergic neurons of the substantia nigra pars compacta. The resultant effect of this is remarkable symptomatic improvement often termed as “response to Levodopa”. This response can be tested in a therapeutic challenge and can be helpful in making a diagnosis of PD **(see Table 1-3).** The side effects of Levodopa include nausea and hypotension which are due to the peripheral effects of dopamine. This can be avoided by decarboxylase inhibitors (carbidopa and benserazide) which would enable delivery of dopamine centrally. Other adverse effects of Levodopa include hallucinations, sleepiness, confusion and impulse control disorders such as gambling, compulsive shopping and hypersexuality (Beaulieu-Boire I and Lang AE, 2015). In addition, the greatest drawback of Levodopa use is the development of worsening motor features with prolonged use. These are a resultant effect of the interruption in the phasic stimulation of the dopaminergic receptors in the striatum, as opposed to the physiological steady supply of dopamine leading to dyskinesia, fluctuations, dystonia and wearing-off (Olanow CW et al., 2006). Severity of dopaminergic neurodegeneration (increased severity increases the risk), dose of Levodopa (daily dose >400mg), female gender and low weight (dose per kilogram) are factors

which are linked to the development of motor complications in response to treatment with Levodopa (Warren Olanow C et al., 2013). In order to reduce these motor complications, an extended-release carbidopa-levodopa formulations (IPX066) have been developed and approved for treatment in people with PD (Dhall R and Kreitzman DL, 2016). But as PD progresses, when these motor complications become troublesome and disabling and unresponsive to classical pharmacologic treatment, levodopa can be administered as a levodopa-carbidopa gel directly into the duodenum through a gastrostomy catheter. Although this formulation has been proven to reduce motor complications, it is limited by adverse effects linked to the surgical procedure and infusion system (Fernandez HH and Odin P, 2011). Continuous subcutaneous infusion, inhaled formulation, levodopa prodrug (XP21279) (LeWitt PA et al., 2014), extended-release levodopa (DM1992) are other levodopa formulations which are currently being investigated to combat motor fluctuations.

- **Dopamine agonists:** Dopamine agonists are not as effective as levodopa in reversing the motor features of PD but are associated with reduced risk of motor complications as dyskinesia. They stimulate the postsynaptic dopamine D1-3 receptors directly in the striatum without the need for further metabolism within the dopaminergic neurons. In early stage of the disease, dopamine agonists may be used as monotherapy or in combination with levodopa. Adverse effects of dopamine agonists are similar to levodopa but also include excessive daytime sleepiness, leg oedema and increased impulse control disorders. Dopamine agonists include Ropinirole and pramipexole which

are oral medications; rotigotine is a transdermal patch used once a day; Apomorphine can be administered subcutaneously as an injection for acute episodes of “off” or as continuous infusion due to its short duration of action. It is most useful in controlling troublesome motor fluctuations which occur in advanced PD (Blandini F and Armentero MT, 2014). Inhaled (VR040) (Grosset KA et al., 2013) and sublingual (APL-130277) (Hauser RA et al., 2016) formulations are other formulations of apomorphine which are currently being investigated.

- **Monoamine oxidase B (MAO-B) inhibitors and safinamide**

  The mechanism of action of MAO-B inhibitors involves reduction of dopamine metabolism which leads to prolonged and sustained stimulation of the dopaminergic receptors. MAO-B inhibitors are used in the treatment of early or mild PD because they are associated with fewer complications than levodopa but offer modest symptomatic improvement. They are also used in advanced disease in combination with other medications to reduce requirements for levodopa and motor fluctuations. Rasagiline and selegiline are irreversible MAO-B inhibitors used in the treatment of PD. Early treatment with MAO-B inhibitor in clinical trials appeared to slow the need for additional dopaminergic treatment and delay motor deterioration suggesting alternative mechanisms of neuroprotection which have been hypothesized. It is speculated that MAO-B inhibitors possess neuroprotective mechanisms which involve prevention of production of reactive oxygen species, increase in neurotrophic and anti-apoptotic factors. However, they have not been shown to alter the natural course of PD (Robakis D and Fahn S, 2015).

A new reversible MAO-B inhibitor is Safinamide. In addition to being used for the treatment of motor fluctuations, it has also been shown to improve motor symptom control in advanced PD (Schapira AHV et al., 2017).

- **Catechol-*O*-methyl transference (COMT) inhibitors**

  The metabolism of levodopa is performed by COMT enzymes in the presence of a decarboxylase inhibitor. Inhibition of these enzymes increases the half-life of levodopa and so used in combination with levodopa for treatment of PD (Muller T, 2015). Several studies have reported that COMT inhibitors such as tolcapone, entacapone and opicapone can increase the half-life of Levodopa, thereby increasing its bioavailability and effectiveness (Hayes MT, 2019, Poewe W and Antonini A, 2015). These medications are used as an adjunct, add-on or adjunct therapy to levodopa in the treatment of motor fluctuations particularly in advanced PD. This is a common first line approach in the treatment of PD (Stowe R et al., 2010). Tolcapone which is used with caution as it causes fatal liver failure; entacapone and opicapone have been recently approved for use in Europe.

- **Amantadine**

  Amantadine is an antiparkinsonian medication and an *N*-methyl-D-aspartate-type (NMDA) glutamate receptor antagonist which has anticholinergic activity (Hubsher G et al., 2012). Even though data on its use in the control of dyskinesia is conflicting (Crosby NJ et al., 2003, Pahwa R et al., 2006, Fox SH et al., 2011), amantadine is used in the treatment of motor features and motor complications in PD. A remarkable decrease in levodopa-induced dyskinesia and “off” time

improvement was demonstrated in a randomized controlled trial of amantadine extended-release capsules (Oertel W et al., 2017). Other similar medications which are currently being evaluated for use in the treatment of dyskinesia include glutamate receptor modulators such as NEU-240, dipraglurant, mavoglurant and foliglurax and adenosine 2a receptor modulators (tozadenant, fipamezole). In Japan, istradefylline, a 2a receptor modulator has been approved while preladenant, another 2a modulator did not show clinical effectiveness (Stocchi F et al., 2017).

- **Other drugs used in Parkinson' s disease**

  Anticholinergic medications such as trihexyphenidyl, benztropine, biperiden and orphenadrine improve tremor but their use is limited because they cause cognitive impairment. On the contrary, treatments that improve cholinergic transmission such as rivastigmine, donepezil and galantamine which are acetyl cholinesterase inhibitors were reported in a recent meta-analysis to increase tremor and incidence of drug side effects but improved cognitive function and behavioural problems (Pagano G et al., 2015).

  Another therapeutic target in PD is the serotonin (5-HT) transmission. Buspirone is currently undergoing clinical trial for treatment of motor complications following informal reports of its use in the treatment of dyskinesia in PD. It is both a 5-HT1A and alpha1-adrenergic receptor agonist also used in the treatment of depression. Pimavanserin, a 5-HT2A inverse agonist has recently been approved for the treatment of psychosis induced by dopamine (Lyons KE et al., 2019). Varenicline (partial alpha-4-beta2 agonist and full alpha7 agonist) and droxidopa (noradrenaline precursor) are medications which are being investigated

for use in treatment of gait, falls and impairment of balance in PD (Balestrino R and Schapira AHV, 2019).

1.2.5.2 Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is an alternative treatment option in people with advanced PD. It involves the use of long-term, direct high frequency electrical current targeted (based on clinical symptoms) at either the subthalamic nucleus-STN (most targeted site), the globus pallidus internus or the thalamus. Although the mechanism of action of DBS seems to involve both excitatory and inhibitory effects, it is speculated that the therapeutic effects of DBS are brought into play by the dissociation of the input and output signals within the stimulated target and the disruption of abnormal information flow through the corticobasal ganglia loop (Chiken S and Nambu A, 2016).

Randomized control trials have shown that in patients with advanced PD, subthalamic nucleus (STN) DBS is better than pharmacological treatment in ameliorating motor complications and improving health-related quality of life (Deuschl G et al., 2006). In addition, STN DBS is effective in the control of motor symptoms and complications, some non-motor symptoms, decreasing disability and reducing the dose of antiparkinsonian medication use (Deuschl G et al., 2006). As good as it is, DBS has its drawbacks. The adverse effects are related to surgical procedure (intraoperative) and hardware malfunction. Others include psychiatric symptoms, worsening of cognitive function, ocular and speech problems.

1.3 Clinical course of Parkinson's disease

Parkinson's disease is a slowly progressive disease with disabling

complications resulting in economic, emotional and social burdens for patients,

their families, caregivers, healthcare system and the society (Singer E, 1973, Whetten-Goldstein K et al., 1997, Rubenstein L et al., 1997, Dodel R et al., 1998, Scheife RT et al., 2000, Guttman M et al., 2003). As at the time of this review, there are only available symptomatic treatments for people with PD, but these do not stop neurodegeneration. In the early stages of the disease, pharmacological treatment provides significant symptomatic control. However, as the disease progresses into the late stages, some symptoms become resistant to levodopa resulting in increasing disability in advanced disease. These symptoms include falls leading to fractures, freezing, dysphagia and choking, hallucinations, dementia, daytime sleepiness and urinary problems (Roberts H and Overstall P, 2008, Balestrino R and Schapira AHV, 2019). In addition, complications from pharmacological treatment also add to the difficulties of treatment in late stage disease (Balestrino R and Schapira AHV, 2019) and may lead to hospitalisation or death. People with PD have severe disability in advanced disease, reduced life expectancy and increased risk of all-cause mortality (Ishihara LS et al., 2007, Xu J et al., 2014). Most patients in the advanced stage of PD lose autonomy, become hospitalised, get placed in nursing homes and death ensues (Goetz CG and Stebbins GT, 1993, Aarsland D et al., 2000).

1.4 Hospitalisation among people with Parkinson's disease

People with PD are usually managed as outpatients in either general neurology clinics, movement disorder clinics (run by neurologists or geriatricians with special interest) or GP practices. However, worsening features of PD, comorbidities and other complications lead to frequent emergency room visits

and subsequent hospital admissions resulting in increasing use of inpatient services (Parashos S et al., 2002, Oguh O and Videnovic A, 2012). People with PD require frequent administration of their medications throughout the day to cope with activities of daily living (Parashos S et al., 2002). During hospitalisation, people with PD encounter multiple challenges with administration of their drug regimen. These challenges range from missed doses to delayed administration of the correct dose of antiparkinsonian medications which could result from the attending hospital staff who may not be familiar with such strict regimen by a patient (Gallagher R et al., 2008, Wu L et al., 2009, Oguh O and Videnovic A, 2012). Freezing, worsening mobility and motor complications may arise from cessation or delay in administration of the required antiparkinsonian medications (Oguh O and Videnovic A, 2012).

Hospitalisation of people with PD may also be complicated by hospital acquired infections (pneumonia, urinary tract and skin infections), deep vein thrombosis (DVT) and autonomic instability such as orthostatic hypotension and syncope (Oguh O and Videnovic A, 2012). People with PD are reported to have increased salivation and silent aspiration (major cause of death) leading to increased risk of chest infections during an admission (Nobrega AC et al., 2008). This may lead to death if aspiration precautions are not enforced during hospitalisation. Although the incidence of DVT is unknown in hospitalised patients with PD, the risk of DVT is increased in these patients due to reduced mobility and being frequently confined to bed. This could lead to pulmonary embolism, a common cause of death in PD. These many challenges may affect the outcome of people with PD during hospital admission (Oguh O and Videnovic A, 2012). As a result, increased mortality, bedsores, falls,

deterioration of motor features, transfer to homes and wound infections have been reported as common outcomes of admission among people with PD (Tan L et al., 1998, Gerlach OH et al., 2013, Skelly R et al., 2014, Mahajan A et al., 2016, Lertxundi U et al., 2017, Paul BS et al., 2017). It is therefore important to recognize and address the reasons for hospitalisation and proffer preventive strategies to hospital admission (Oguh O and Videnovic A, 2012, Koay L et al., 2018). This was the focus of my systematic review **(See Chapter 2).**

1.5 Mortality in Parkinson's disease

The introduction of levodopa more than forty years ago for the treatment of PD has led to an effective means of improving some symptoms of the disease (Williams-Gray CH et al., 2013). However, data on some aspects of prognosis of PD such as disease progression, survival and mortality remain largely variable despite major breakthroughs in the understanding of genetics and pathophysiology of PD. Standard treatments do not seem to control most non-motor features but rather exacerbate them in some instances. Although PD has a complex pathology involving extensive areas of the peripheral nervous system, the brain and affecting many neurotransmitter systems in varying patterns and variable rate of spread, one major issue is that current available treatment is targeted only towards replacement of the dopaminergic nigrostriatal deficit (Williams-Gray CH et al., 2013). Further information on the natural history of PD is however required to understand PD prognosis. Such information is important to patients, their families and care givers particularly when planning treatment. In addition, healthcare service planning and designing of clinical trials can be improved with availability of data on PD

prognosis. If this information is incorporated into a prognostic model, knowledge of predictors of poor prognosis may allow individually tailored predictions and enable targeted treatment of people with PD (Macleod AD et al., 2014).

Mortality is an important aspect of PD prognosis which requires better understanding. Although people with PD have been reported to have a shorter life expectancy compared to the general population, mortality rates ratios vary considerably between studies ranging from 0.9 to 3.8. This variability is probably explained by variable methodology, recruitment setting and patient selection (Macleod AD et al., 2014). Current available prospective studies on mortality and disease progression were conducted using data from selected cohorts recruited in clinical trials (Poewe W, 2006). Some of these studies have recruited PD cases based on certain clinical criteria and randomly assigned them into groups based on drug treatment: low-dose levodopa versus low-dose bromocriptine resulting in a cohort which is not truly representative of PD within the population (Hely MA et al., 2008).

Previous population-based studies, rather than more informative incident cohorts followed-up from diagnosis, used prevalent cohorts with varying disease duration leading to possible overestimation of mortality (Berger K et al., 2000, Fall PA et al., 2003, Hobson P and Meara J, 2004, de Lau LML et al., 2005, D'Amelio M et al., 2006, Buter TC et al., 2008, Posada IJ et al., 2011). Other population-based studies which have employed incident cohorts have included patients with corticobasal degeneration, progressive supranuclear palsy and multiple system atrophy which are known to have higher morbidity

and mortality (Herlofson K et al., 2004). In addition, a recent study with a follow-up of ten years used incident PD cases which were recruited from a movement disorder clinic raising questions about selection bias and representativeness (Auyeung M et al., 2012). Furthermore, a recent systematic review (Macleod AD et al., 2014) reported that synthesis of mortality data in their review was hampered by poor quality of available studies, heterogeneity in methodology and study participants. They however recommended that future high-quality studies should be performed and should at a minimum have the following characteristics: [1] use incident PD cohort; [2] use population-based cohort; [3] use validated diagnostic criteria and expert confirmation of diagnosis; [4] use exclusion criteria which applies only to diagnostic accuracy; [5] use prospectively followed-up cases; and [6] use diagnosis as baseline for analysis. In order to mitigate these issues, a study of incident PD cohort with follow-up from diagnosis and using a more modern dataset which is representative of UK population (The Health Improvement Network- a large primary care database (discussed in detail in Chapter 3) is required to study mortality of PD. Hence the need for this study.

In addition, whilst it is likely that the introduction of levodopa-containing medication reduced mortality compared to the pre-levodopa era, there are no robust data to establish this effect (Macleod AD et al., 2014, Xu J et al., 2014). There is therefore a need to accurately estimate mortality among people with PD in comparison to the general population using a large UK primary care database (THIN) while accounting for confounding factors (age, gender, smoking and social deprivation). These will allow for better prognostication and

target treatment for potential factors linked to mortality resulting in a better quality of life and improved survival in people with PD.

1.6 Overall plan for this thesis

Parkinson's disease is associated with multiple complications as the disease progresses resulting in increased hospitalisation and increased death rate compared to the general population. There is a paucity of data on hospitalisation of people with PD in the UK and there are few studies which have investigated mortality of people with PD over time since 2006 (post levodopa era). Previous research studies on mortality are also limited by heterogeneity in methodology and representativeness (**see Section 1.5)**. In order to explore hospitalisation and mortality in PD, primary care electronic databases are a rich source of data. The large size and generalisability of the databases makes them suitable for investigating incidence of PD in the general population; the risk for hospitalisation and for mortality of people with PD in comparison to people without PD from the UK general population, and potential factors associated with an increase in these risks. Additionally, the database can show regional variations in the diagnosis of PD in the UK due to the geographical layout of the practices contributing data to the database. Furthermore, longitudinal analysis of data following the diagnosis of PD is possible due to the continuous update of the healthcare data. The electronic medical records and its use and advantages in research are well recognised and will be described in more detail in chapter 3, alongside its limitations.

This thesis aims to explore using prospectively collected electronic medical records in primary care, with a view to characterising hospitalisation and

mortality in PD and identify contributing factors. This will be achieved through a series of four studies. The first study is a systematic review describing the factors/reasons for hospitalisation among people with PD. For the other three studies, data from The Health Improvement Network (THIN), a primary care electronic medical records database will be used to:

1. Investigate the incidence of PD diagnosis in the UK over time and between different geographical and demographic groups.
2. Examine the rate of mortality of people with PD in UK primary care over a period more than a decade and determine factors that increase the risk of death in PD compared to the general population.
3. Explore the rate of hospitalisation and identify the reasons/factors associated with hospitalisation of people with PD in the UK.

1.7 Outline of my thesis

Below is a summarized version of the outline of chapters in this thesis:

Chapter 1: Introduction to the research (see Sections above)

This chapter gives an overview of current knowledge on PD with emphasis on complications leading to hospitalisation and mortality. The aims of the research are also briefly described **(see Section 1.6 above).**

Chapter 2: Systematic Review: **Factors associated with hospitalisation among people with Parkinson's disease.**

This chapter describes a systematic review conducted to investigate factors/reasons associated with hospitalisation in Parkinson's disease.

Chapter 3: The Health Improvement Network (THIN) database.

This chapter gives an overview of electronic medical records and their use in research with emphasis on THIN, which is the data source used in chapters 4 to 6. In this chapter, THIN which is a UK primary care medical record database is compared to other similar UK primary care databases.

Chapter 4: Incidence of Parkinson's disease.

This chapter gives a description of a cohort study using THIN. The study estimates the incidence of PD in the UK between 2006 and 2016. Differences in socio-demographic characteristics of people with an incident recording of PD were explored. Incident cases used in chapters 5 and 6 were identified.

Chapter 5: Mortality in Parkinson's disease: This explores mortality among people with PD compared to those without PD and explores differences by socio-demographic factors. Trends in mortality and mortality in relation to year after diagnosis of people with PD were also explored.

Chapter 6: Rate of hospital admissions and underlying reasons among people with Parkinson's disease:

This chapter describes a cohort study which explored the rate of hospitalisation among people with PD using data from THIN. Sociodemographic differences in hospitalisation among people with PD compared to those without PD were also examined.

Chapter 7: Summary of results and discussion: This chapter provides a summary of the salient findings from the systematic review and the three studies conducted using THIN. The implications of the findings from this

research on clinical and public health practice and policy are discussed. A brief description of future research is also provided in this chapter.

Chapter 2 Factors associated with hospitalisation among people with Parkinson's Disease: A Systematic Review and Meta-analysis

2.1 Chapter overview

In this chapter, I report a systematic review of literature to determine reasons for hospitalisation among people with PD. Findings from this review informed the design of the exploratory study (discussed in chapter 6) on the recording of hospitalisation of people with PD in THIN. This chapter is the foundation of the published paper which is included in **Appendix 2-1** (Okunoye O et al., 2020).

2.2 Study rationale

With disease progression, people with Parkinson's Disease (PD) suffer increasing disability leading to increasing rates of hospital admissions which in turn are associated with poor outcomes (for the patient and carers) and increasing costs on the society (Singer E, 1973, Whetten-Goldstein K et al., 1997, Rubenstein L et al., 1997, Dodel R et al., 1998, Scheife RT et al., 2000, Guttman M et al., 2003). The reasons for hospitalisation among people with PD vary between countries worldwide (Chou KL et al., 2011) and this could be due to differences in the health care systems. Motor complications are a common reason for admission in PD. Similarly, infections, trauma, dehydration, cardiovascular and cerebrovascular emergencies, which are not directly related to PD, have been reported as reasons for admission among people with PD (Temlett JA and Thompson PD, 2006, Guneysel O et al., 2008). Worsening motor complications, falls, cognitive and psychiatric problems also contribute to hospitalisation in PD particularly in advanced disease. A recent systematic

review reported falls, acute decompensation of PD symptoms, cardiovascular problems and infections as the top reasons for hospitalisation among people with PD but did not provide pooled estimates for these reasons (Koay L et al., 2018). This is the first study to my knowledge to present data on rigorous systematic review that synthesized data on pooled prevalence of identified reasons for admission. Identifying factors which are associated with admissions among people with PD may provide a benchmark against which interventions to reduce and prevent hospitalisations can be measured. It could also provide information on what the most common potentially modifiable causes of admissions are, so that interventions can be targeted at preventing these where possible. This could lead to a reduction in the morbidity and mortality associated with PD and decrease the financial burden on the patients, their carers and the healthcare system (Paul BS et al., 2017). The focus of this review was to determine the reasons for hospitalisation among people with PD and provide pooled estimates of prevalence of the common reasons.

2.3 Aim and objectives

2.3.1 Aim

To synthesize pooled estimates of prevalence of the common causes of hospital admission among people with PD.

2.3.2 Objectives

- To systematically review and present available literature on hospital admissions among people with PD.
- To describe the causes of hospital admissions among people with PD.

2.4 Methodology

2.4.1 Search strategy

This involved searching for published academic articles in eleven electronic databases. The review protocol is registered and published on PROSPERO (Record number: CRD42018105102). A pre-specified protocol was followed throughout utilizing the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for the search, data extraction, synthesis and reporting of results and a checklist with the description of where each item is reported in this thesis is provided in **Appendix 2-2** (Moher D et al., 2009).

2.4.2 Search in electronic databases

The search was conducted in eleven electronic databases including Medline and EMBASE using the OVID interface, Wed of Science, Science Citation

Index (SCIE), Cochrane Database of Systematic Reviews (CDRS), Cochrane Central Register of Controlled Trials (CCRCT), PsychINFO, Health Technology Assessment (HTA) database, NHS Health Economic Evaluation Database (HEED), Database of Abstracts of Reviews of Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) initially in April 2018 and later updated in October 2019.

In order to identify relevant articles, search terms were developed based on the PICO (Participants/ Intervention/ Comparison/ Outcome) search strategy (Sayers A, 2007). The "intervention" and "comparison" component were not applicable given the descriptive nature of this study so were excluded in the search. In addition, Medline Medical Subject Headings (MESH) and keywords terms were used where appropriate to maximize the sensitivity of the search. The search was first run using Medline and then all other databases. The syntax for the Medline search is presented in **Appendix 2-3**. Forwards and backwards tracking of references of key articles to identify other relevant studies was carried out. The full search strategy used for the electronic database search is presented in **Table 2-1** and includes terms which are related to the following concepts:

- **Participants**: People with PD
- **Intervention:** Not applicable
- **Comparison:** Not applicable
- **Outcome**: Hospital admission.

2.4.3 Search limits

There were no restrictions to language, PD diagnosis criteria or year of publication. This was to allow retrieval of all available articles with regards to the subject being reviewed.

Table 2-1. Search terms used in electronic databases

Participants: People with Parkinson's disease.	"Parkinson" OR "Parkinsonian disorder" (MESH)
AND	
Outcome: Admission	"hospitalization" (MESH) OR "hospitalisation" OR "Inpatient care" OR "admission(s)" OR "Inpatients" (MESH) OR "patient- admission" OR "patient readmission"

2.4.4 Criteria used for selection and exclusion of studies used for this systematic review

2.4.4.1 Type of studies selected

All original prospective or retrospective studies with any study design were included if they provided data on hospitalisation among people with PD and reported reasons for admission. Studies were considered retrospective if the data were collected by tracking and reviewing patients' paper-based information (Tan L et al., 1998, Klein C et al., 2009) or codes were used to extract PD patients' information from electronic databases (Lertxundi U et al., 2017). Studies were described as prospective studies if they used pre-designed

proforma for collection of data on admissions among people with PD (Vossius C et al., 2010, Paul BS et al., 2017).

2.4.4.2 Type of studies excluded

Articles were excluded:

- If they did not report data on hospital admissions among people with PD.
- If they did not report reasons for hospitalisations among people with PD.
- If they did not report the number PD patients admitted.
- If the exact number of PD patients admitted for each reason was not provided.

2.4.5 Type of study participants

Studies were included:

- if the participants had PD as described by the authors.
- if the participants had data on any form of hospital admission.

2.4.6 Type of study setting

Studies were included if they were hospital-based or population-based studies. When information was collected from PD patients attending a hospital, the setting was termed hospital-based. Community-based prevalence studies or studies which involved national databases were designated population-based (Vossius C et al., 2010, Kelly B et al., 2016).

2.4.7 Types of outcome measures

Studies were included if they reported data on both primary and secondary outcomes described:

2.4.7.1 Primary outcome: any hospital admission

2.4.7.2 Secondary outcomes:

- Reasons for hospital admission for example pneumonia or fall/fractures.
- Number of people with PD admitted to the hospital.
- Number admitted for the reason given for example number admitted for pneumonia or falls.

2.4.8 Data collection

Following the search, citations of the articles retrieved were downloaded, indexed and deduplicated using EndNote version X8. One reviewer (OO) did the initial screening by reviewing title and abstracts of all articles to identify studies which were potentially relevant using the inclusion criteria. Thereafter, the retrieved full text articles of all potentially eligible studies were independently read as a whole and grouped by two reviewers (OO and GK) into two categories: [1] “included” and [2] “excluded”. Discrepancies in grouping the studies were settled through discussions with the team (OO, GK, KW and AS). Studies excluded with reasons are documented and summarized in **Section 2.5.1** and **Appendix 2.4.**

2.4.9 Quality assessment of studies

Since systematic reviews and meta-analyses are considered the highest level of evidence in science, the quality assessment of included studies is key to allow a clear picture of the evidence base (Dreier M, 2013, Burns PB et al., 2011). The Newcastle Ottawa Scale (NOS) was used since it was anticipated that most the studies included would be cohort studies (Wells G et al., 2015). In

as much as the focus of this systematic review and meta-analysis is hospital admissions among people with PD and most studies likely to be cohort in nature, the case-control version of the scale was used for the case-control studies that provided data of interest. The Newcastle Ottawa scale is one of the most widely used tools for assessing quality and risk of bias in observational studies (Luchini C et al., 2017). It comprises of eight specific items addressing three quality parameters including selection, comparability and outcome. Except for the comparability which can be modified based on the variable of interest to score up to two, each item on the scale is scored one point (Wells G et al., 2015).

The quality of the components of each included study was assessed at different times by two reviewers (OO and GK). The reviewers assigned “0” or “1” on whether the specified item had been addressed in the study. Each reviewer was given a scoring manual with criteria on what should be assigned a score of “0” or “1” **(Appendix 2-5)**. Where necessary, disagreements were settled through discussion with the team (OO, GK, KW and AS).

Each of the studies included was given a total potential score of 0 to 9, with 0 to 3 representing low quality (indicating high risk of bias); 4 to 6 representing moderate quality and 7 to 9 representing high quality study (Wells G et al., 2015). However, given the paucity of available data, studies were not excluded on the basis of quality or risk of bias. The results of this quality assessment of all included studies are presented in **Section 2.5.5**.

2.4.10 Data extraction

Data of interest were captured from included studies using a standardized data extraction form. These included:

- General study characteristics: study author(s), year of publication, cohort/study name, study design, country, study population/setting (hospital/population based).
- Sociodemographic characteristics of study participants: proportion of males and females, mean age of patients and controls
- Information on hospitalisation: total number of admissions, mean length of hospital stay, reasons for admission, number of people admitted for the different reasons provided and outcome of hospitalisation if reported.
- Other information: type of statistical analysis done; interventions/preventive strategies provided.

Data were extracted and entered into an Excel spreadsheet by one reviewer (OO). The extracted data in the Excel spreadsheet was reviewed by AS to ensure that extracted data were correct. All included studies had required data, so I did not have to contact authors for more data.

2.4.11 Data analysis

In clinical practice and public health, systematic reviews of available data with regards to the benefits and risks of medical intervention, can inform decision making (Chalmers I et al., 1992, Mulrow CD, 1994). Such reviews are based on meta-analysis, whenever possible.

In the last two decades, meta-analysis has become widely accepted as the top position on the hierarchy of evidence. It is a statistical analysis which integrates and combines the results of many independent studies which are considered by the researcher to be “combinable” thus increasing power (Huque M, 1988, Duval S and E. W, 2011). However, there are rising challenges of heterogeneity and biases in publications (Duval S and E. W, 2011). A study with a statistically significant result is likely to be published by a scientific journal leading to more significant findings being published. This causes publication bias in the meta-analysis of published articles (Begg CB and Berlin JA, 1988, Stern JM and Simes RJ, 1997, Kicinski M et al., 2015). Such bias may lead to inaccurate conclusions of systematic reviews if not detected (Sutton AJ et al., 2000).

One way of measuring publication bias in meta-analysis is by examining the asymmetry of the funnel plot (though subjective due to visual examination). This usually presents effect sizes plotted against their precisions or standard error (Light JR and Pillemer BD, 1986, Sterne JAC and Egger M, 2001). Second is to use statistical tests such as Begg’s rank test (Begg CB and Mazumdar M, 1994) or Egger’s regression test (Egger M et al., 1997) in the funnel plots.

In this study, Egger’s test was used. It regresses the standardized effect sizes on their precisions. The regression intercept is expected to be zero in the absence of publication bias.

The pooled prevalence of the common reasons for admission among people with PD was calculated through a meta-analysis. For this analysis, the exact number of people with PD in an entire cohort and the number admitted for each reason was extracted from each included study and used.

The possibility of bias within the included studies that reported the top reasons for admission among people with PD was assessed using the Egger's test. The results of this analysis are presented in **Section 2.5.4** and **Appendix 2.6.**

2.4.12 Data synthesis

In order to provide a descriptive synthesis of all studies included in this review, extracted data from the studies were summarised in tables. Tables were used to present information such as: general characteristics of included studies; reasons for admission as reported in the studies included: data used for analysis and results of analysis.

2.5 Results

2.5.1 Selection processes

The electronic search of eleven databases retrieved a total of 7283 citations. After removing 2436 duplicates, EMBASE search retrieved 2908 citations, Medline search retrieved 847, Cochrane databases (CDRS, CCRCT, HTA, DARE, HEED) search retrieved 440, Web of Science (plus SCIE) retrieved 250, PsychINFO retrieved 170 and CINAHL search retrieved 232 resulting in a total of 4847 citations for screening. Of the 4847 citations and abstracts retrieved, 4782 were excluded following screening by title and abstract. The reasons for excluding each article were noted. Thereafter, full text articles of 65 citations

were reviewed and assessed for eligibility. Of these, 56 articles were excluded with reasons provided in **Appendix 2-4.** Twenty-three (Guttman M et al., 2004, Woodford H and Walker R, 2005, Cosentino M et al., 2005, Temlett JA and Thompson PD, 2006, Louis ED et al., 2007, Derry CP et al., 2010, Vossius C et al., 2010, Chou KL et al., 2011, Gerlach OHH et al., 2012, Willis AW et al., 2012, Walker RW et al., 2014, Martinez-Ramirez D et al., 2015, Low V et al., 2015, Kelly B et al., 2016, Martins J et al., 2016, Gil-Prieto R et al., 2016, Mahajan A et al., 2016, Shahgholi L et al., 2017, Harris M and Fry M, 2017, Lertxundi U et al., 2017, Muzerengi S et al., 2017, Merola A et al., 2018, Hobson P et al., 2019) of the 56 potentially eligible articles excluded, reported reasons for hospitalisation but failed to provide data on exact number of people admitted for the reasons they reported so were excluded **(Appendix 2-7).** Finally, nine studies (Kessler II, 1972, Tan L et al., 1998, Martignoni E et al., 2004, Guneysel O et al., 2008, Klein C et al., 2009, Skelly R et al., 2014, Braga M et al., 2014, Lubomski M et al., 2014, Paul BS et al., 2017) were considered eligible from the systematic search and included in the review and meta-analysis **(Figure 2-1).**

2.5.2 General characteristics of selected studies

Following the systematic search, nine articles were included. These articles provided data on all the outcomes investigated. Seven studies originally set out to investigate hospitalisation as well as provide reasons for hospitalisation among people with PD while the two other studies included admissions as a sub-analysis.

Six of the included studies (Kessler II, 1972, Tan L et al., 1998, Guneysel O et al., 2008, Klein C et al., 2009, Braga M et al., 2014, Lubomski M et al., 2014) were retrospective while three (Martignoni E et al., 2004, Skelly R et al., 2014, Paul BS et al., 2017) were prospective studies. Three studies were from Europe (Martignoni E et al., 2004, Skelly R et al., 2014, Braga M et al., 2014), two from the Middle East (Guneysel O et al., 2008, Klein C et al., 2009) and one each from Asia (Tan L et al., 1998), Australia (Lubomski M et al., 2014) and India (Paul BS et al., 2017).

Eight of the nine studies were hospital-based studies with most settings being neurology, general medicine and emergency departments. One (Lubomski M et al., 2014) included study was population-based **(Table 2-2).**

Figure 2-1. Diagram of the selection procedure to identify articles included in the systematic review and meta-analysis.

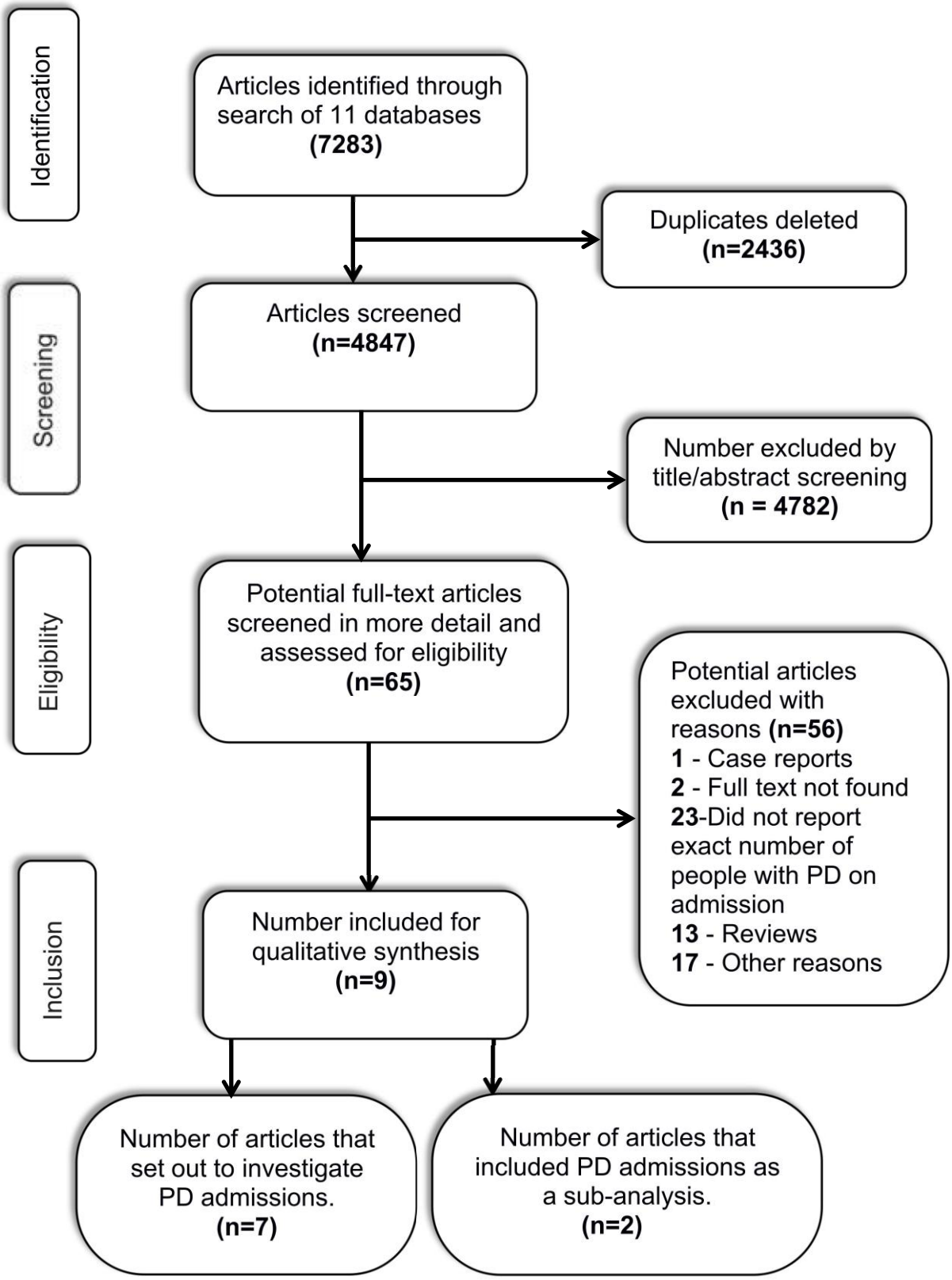


Figure 2-1 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1.

Table 2-2. General characteristics of included studies.

Study	Year	Country	Study design	Aim of study	Cohort	Mean Age of PD cases	Female (%)	Main reasons for admission reported
Paul BS et al	2017	India	Prospective	Analyse causes for hospital admission	146	68.5	33.3%	Motor features & Levodopa related motor features, Infections, encephalopathy, fractures
Lubomski et al	2014	Australia	Retrospective	Examine patterns of acute care hospitalisation of Parkinson's disease cases	5637	75	37.2%	Falls/fractures, Cardiovascular problems, dementia.
Braga et al	2014	Italy	Retrospective	To detect co-morbid conditions in large population of Parkinson's disease (PD) cases.	295	76.7	Not reported	Neuropsychiatric disorders, cardiovascular problems, infections, medical problems, trauma-fracture.
Skelly et al	2014	United Kingdom (Derby)	Prospective	To confirm that care on a specialist in-patient PD Unit (SPDU) would improve outcomes of urgent medical care among PD cases.	44	81	26.5	PD symptoms, LRTI/pneumonia, UTI, postural hypotension.
Klein et al	2009	Israel	Retrospective	Review reasons for admission of PD cases to neurological department.	143	69.5	55	PD-motor and non-motor problems, falls, infections.
Guneysel et al	2008	Turkey	Retrospective	To determine reason for emergency admission	76	73.2	28	Infections (pneumonia, UTI), trauma(falls/fracture), Cardiovascular co-morbidities
Matignoni et al	2004	Italy	Prospective	To investigate acute comorbid events prompting hospitalisation	180	75.6	88	Drug monitoring, trauma, cardiovascular disorders, medical problems.
Tan et al	1998	Singapore	Retrospective	To provide profile of PD patients who required hospital admission	173	74.7	80	Uncontrolled PD symptoms, chest infections, urinary dysfunction, falls.
Kessler et al	1972	USA	Retrospective	Epidemiologic studies in PD.	468	Not reported	46	PD symptoms, cardiovascular, respiratory & digestive system problems.

Table 2-2 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1.

2.5.3 Reasons for admission

Reasons for hospital admissions among people with PD were variably categorized by the authors. When the reasons were described as directly related to PD, they were referred to as “PD related” and when the reasons were described as indirectly related to PD, they were reported as non-PD related (Kessler II, 1972, Tan L et al., 1998, Martignoni E et al., 2004, Klein C et al., 2009, Skelly R et al., 2014, Lubomski M et al., 2014). Two studies made no distinction (Guneysel O et al., 2008, Braga M et al., 2014).

Reasons directly related to PD as reported by the authors were mostly motor features. These included uncontrolled motor features, prolonged “off” and frequent freezing, “On” and “Offs”, fluctuations and dyskinesias. Reasons which were classified as non-PD related included: cardiovascular comorbidities such as congestive cardiac failure, arrythmias, angina, ischaemic heart disease/acute coronary syndrome; infections (pneumonia and urinary tract infection); gastrointestinal issues: constipation, dysphagia, nausea and vomiting; cerebrovascular accident, transient ischaemic attack; syncope, postural hypotension; falls/fractures; encephalopathy, delirium, electrolyte imbalance; neoplasms; neuropsychiatric problems: hallucinations and depression. A table summarizing the reasons for admission among people with PD is available in **Appendix 2-8.**

The main reasons for hospitalisation among people with PD reported by all nine included studies were 1) Infections (pneumonia and urinary tract infection); 2) gastrointestinal disorders; 3) falls/fractures; 4) PD related motors symptoms; 5)

neuropsychiatric problems and 6) cardiovascular comorbidities. This is summarized in **Table 2-3.**

Table 2-3. Main reasons for hospital admissions in included studies.

	Paul BS et al (2017)	Lubomski et al (2014)	Braga et al (2014)	Skelly et al (2014)	Klein et al (2009)	Guneysel et al (2008)	Matignoni et al (2004)	Tan et al (1998)	Kessler et al (1972)	I^2 (%)
Neuropsychiatric problems (hallucinations, psychosis & depression)	✓	✓	✓		✓		✓	✓	✓	95.45%
Worsening motor features	✓	✓		✓	✓		✓	✓	✓	94.61%
Infections (urinary tract infection & pneumonia)	✓	✓	✓	✓	✓	✓	✓	✓		93.11%
Gastrointestinal complications (constipation, dysphagia, nausea and vomiting)		✓	✓		✓	✓	✓	✓	✓	93.07%
Cardiovascular co-morbidities (heart failure & acute coronary syndrome)	✓	✓	✓			✓	✓	✓		86.7%
Falls & fractures	✓	✓	✓		✓	✓	✓	✓		78.65%

Table 2-3 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1.

2.5.4 Quality assessment

Three of the included studies were assessed using the case-control NOS scoring while the remaining six were assessed using the cohort NOS scoring. All included studies had clear inclusion criteria and most cases had a diagnosis of PD confirmed by diagnostic criteria or a neurologist. This ensured adequate case definition, representation of cases/cohort and exposure ascertainment (question 1, 2 and 6 for NOS scoring of case-control studies; question 1 and 3 for NOS scoring of cohort studies). Although three studies had a clear control definition (question 4 for scoring case-control studies), only two out of the nine studies demonstrated adequate control/unexposed cohort selection indicating the possibility of selection bias (question 3 for scoring case-control studies; question 2 for scoring of cohort studies). In addition, two out the three case-control studies reported clear ascertainment of control (question 7).

In terms of comparability between cases and controls and exposed and non-exposed cohort, only two out of nine studies demonstrated clear comparability based on age, gender, ethnicity and year of admission, and the other seven studies were prone to selection bias (question 5 for both case-control and cohort studies' NOS scoring).

All cohort studies had clear outcome assessment (question 6) and fairly adequate follow up of cohort (question 8) indicating low risk of bias with regards to follow up. Response rate was reported in two out of the three case-control studies indicating poor follow up and risk of bias (question 8).

There was evidence of selection bias among included studies, but no studies were excluded on the basis of the quality assessment due to paucity of information. The results of the quality assessment of all included studies are summarized in **Appendix 2-9.**

2.5.5 Data analysis

2.5.5.1 Prevalence of the common factors for admission in Parkinson's disease

In order to calculate the pooled prevalence of the common reasons for hospital admissions among people with PD through a meta-analysis, data from all nine (Kessler II, 1972, Tan L et al., 1998, Martignoni E et al., 2004, Guneysel O et al., 2008, Klein C et al., 2009, Skelly R et al., 2014, Braga M et al., 2014, Lubomski M et al., 2014, Paul BS et al., 2017) included studies were used. These data included: the exact number of people with PD in the study cohort and the number admitted for each reason (for example, number admitted for falls/fractures or infections or worsening motor symptoms or cardiovascular, gastrointestinal or neuropsychiatric problems) associated with hospitalisation among people with PD. These data are summarized in **Table 2-4**.

Based on each reported factor, the overall I^2 values for all nine studies was high suggesting significant heterogeneity between studies. Studies which reported neuropsychiatric problems, worsening motor symptoms of PD, infection and gastrointestinal problems had the highest I^2 values of 95.45%, 94.61%, 93.11%, 93.07% respectively. In addition, studies which reported cardiovascular comorbidities had I^2 value of 86.70% and those which reported

falls/fractures had an I^2 values of 78.63%. This is summarized in **Tables 2-4 and 2-5.**

The pooled prevalence of infections among eight studies was 22% (95%CI: 16% to 30%) **(Figure 2-2)**; worsening motor symptoms of PD among seven studies was 19% (95%CI: 13% to 27%); falls/fractures among seven studies: 18% (95%CI: 14% to 21%); cardiovascular comorbidities among six studies was 13% (95%CI: 9% to 18%); neuropsychiatric symptoms among seven studies was 8% (95%CI: 4% to 13%) and that of gastrointestinal problems among eight studies was 7% (95%CI: 4% to 11%). This is summarized in **Table 2-4 and Table 2-5 and Appendix 2-6.**

2.5.5.2 Publication bias

Egger's test revealed no evidence of publication bias in all study outcomes (all p>0.05) except for worsening motor symptoms of PD (p=0.013). This explanation for this could be the significant heterogeneity of the study population **(Table 2-5 and Appendix 2-6).**

Table 2-4. Data used for meta-analysis.

	No of PD pts with falls		No of PD pts with infections (UTI & pneumonia		No of PD pts with worsening motor features		No of PD pts with cardiovascular co-morbidities		No of PD pts with Gastro-intestinal Problems		No of PD pts with Neuro-psychiatric complications		Total no of PD cases in the study
	n	%	n	%	n	%	n	%	n	%	n	%	N
Paul BS et al (2017)	13	8.9	25	17.1	47	32.2	18	12.3	3	2.1	4	2.7	146
Lubomski M et al (2014)	1116	19.8	1149	20.4	569	10.1	941	16.7	749	13.3	766	13.6	5637
Braga et al (2014)	47	15.9	59	20			29	9.8	16	5.4	18	6.1	295
Skelly et al (2014)			25	56.8	6	13.6							44
Klein et al (2009)	30	21	22	15.4	29	20.3			5	3.5	22	15.4	143
Guneysel et al (2008)	21	27.6	24	31.6			11	14.5	6	7.9			76
Matignoni et al (2004)	21	11.7	7	3.9	37	20.6	11	6.1	4	2.2	11	6.1	180
Tan et al (1998)	39	22.5	59	34.1	40	23.1	41	23.7	34	19.7	27	15.6	173
Kessler et al (1972)					91	19.4			45	9.6	10	2.1	468
Total no of articles with data on reason for admission	7		8		7		6		7		7		
I^2	78.63%		93.11%		94.61%		86.70%		93.07%		95.45%		

n-number, N-total number. Table 2-4 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1.

Table 2-5. Prevalence of the common factors for admission in PD.

Topmost factors for admission	I^2 (%)	Publication bias	Estimated Pooled prevalence (%)	Estimated Pooled prevalence (95% CI)	p-value	Studies
Infection (urinary tract infection & pneumonia)	93.11	0.597	22	16-30	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Braga M et al., 2014, Skelly R et al., 2014, Klein C et al., 2009, Guneysel O et al., 2008, Martignoni E et al., 2004, Tan L et al., 1998)
Worsening motor features of PD	94.61	0.013	19	13-27	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Skelly R et al., 2014, Klein C et al., 2009, Martignoni E et al., 2004, Tan L et al., 1998, Kessler II, 1972)
Falls/fractures	78.63	0.473	18	14-21	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Braga M et al., 2014, Guneysel O et al., 2008, Martignoni E et al., 2004, Klein C et al., 2009)
Cardiovascular co-morbidities (heart failure & acute coronary syndrome)	86.70	0.367	13	9-18	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Braga M et al., 2014, Guneysel O et al., 2008, Martignoni E et al., 2004, Tan L et al., 1998)
Neuropsychiatric complications (Hallucinations, psychosis, and depression)	95.45	0.147	8	4-13	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Braga M et al., 2014, Martignoni E et al., 2004, Tan L et al., 1998, Kessler II, 1972)
Gastrointestinal problems (constipation, dysphagia, nausea & vomiting)	93.07	0.058	7	4-11	<0.001	(Paul BS et al., 2017, Lubomski M et al., 2014, Braga M et al., 2014, Guneysel O et al., 2008, Martignoni E et al., 2004, Tan L et al., 1998)

Table 2-5 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1.

Figure 2-2. Forest plot of articles that reported infections as reason for hospitalisation.

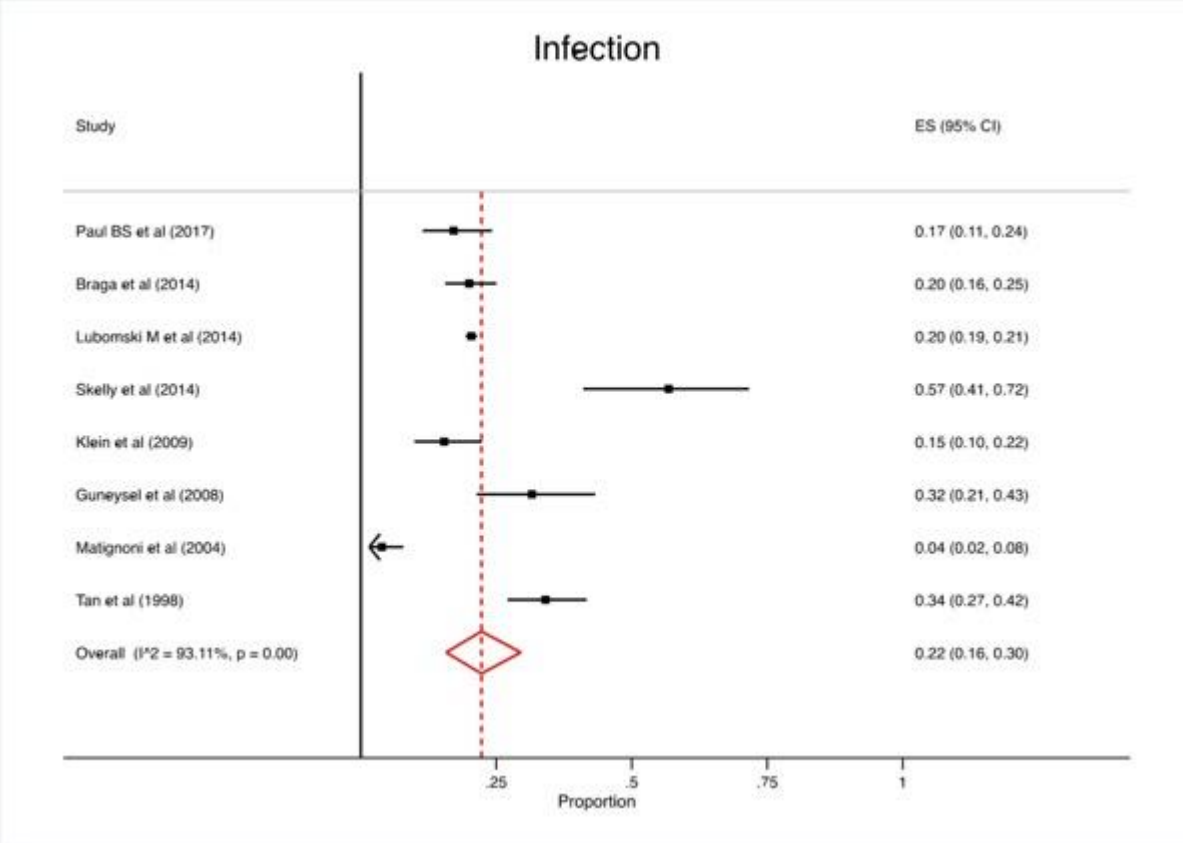


Figure 2-2 was taken from published manuscript by Okunoye et al and is provided in full for reference in Appendix 2-1

2.6 Discussion

2.6.1 Summary of main findings

In this systematic review and meta-analysis, a total of 7283 articles were identified of which nine studies with 7162 people with PD were included. A high degree of heterogeneity was seen between included studies with regards to reasons for hospitalisation among people with PD. The pooled prevalence of the main reasons for hospital admissions among people with PD was 22% (95%CI:16%-30%) for infections (mainly urinary tract infections and pneumonia); 19% (95%CI:13%-27%) for worsening motor manifestations of PD;

18% (95%CI:14%-21%) for falls/fractures; 13% (95%CI:9%-18%) for cardiovascular co-morbidities; 8% (95%CI:4%-13%) for neuropsychiatric and 7% (95%CI:4%-11%) for gastrointestinal complications.

2.6.2 Main reasons for hospitalisation in Parkinson's disease and proffered preventive strategies

The included studies in this review show that major factors associated with hospital admissions among people with PD include: infections mainly pneumonia and urinary tract infection (UTI); worsening motor features of Parkinson's disease; falls/fractures; cardiovascular comorbidities; gastrointestinal (GIT) complications (constipation, dysphagia, nausea and vomiting) and neuropsychiatric problems including hallucinations, psychosis and depression. There was no available meta-analysis or prevalence data for comparison, but these findings are in line with a recent systematic review which reported that 50% of admissions among people with PD are due to falls, acute decompensation of PD symptoms, cardiovascular comorbidities and infections. However, the exact prevalence of these reasons for admission among people with PD was not reported (Koay L et al., 2018).

2.6.2.1 Infection-related hospitalisation

Infection related hospital admissions particularly urinary tract infection (UTI) and pneumonia were the topmost reasons for admission among people with PD. This is in line with data reported by studies where infectious diseases as UTI, aspiration pneumonia and others were identified as main reasons for emergency admissions in PD (Guneysel O et al., 2008, Low V et al., 2015, Fujioka S et al., 2016, Paul BS et al., 2017). On the contrary, other studies

have reported falls/fractures as the topmost reason for admissions in PD. This discrepancy may be that infections are underestimated in some studies, for example UTI may be reported as a urinary disorder and not as an infection. Conversely, a deterioration due to UTI may result in falls among people with PD and this could be wrongly coded as falls instead of UTI (Tan L et al., 1998, Temlett JA and Thompson PD, 2006, Vossius C et al., 2010).

People with PD are reported to be more frequently admitted for infections than the age- and sex-matched control group without PD (Temlett JA and Thompson PD, 2006, Braga M et al., 2014). In terms of underlying reasons, autonomic dysfunction in PD leading to bladder emptying problems can be a source of UTI. In addition, UTI can result from bowel problems causing constipation, faecal impaction and urinary retention and consequent UTI (Campeau L et al., 2011, Oguh O and Videnovic A, 2012).

Pneumonia is one of the main infections associated with hospitalisation in PD identified in this study. It is reported as the leading cause of death among people with end stage PD (Beyer M et al., 2001, Pennington S et al., 2010). With progressing disease, people with PD develop swallowing difficulties, poor cough and poor respiratory effort leading to recurrent aspiration and subsequent pneumonia (Leopold N and Kagel M, 1997, Arasalingam A and Clarke CE, 2014). In order to avoid hospital admissions, these predisposing factors must be identified early and immediately treated.

2.6.2.2 Admissions due to worsening motor features of Parkinson's disease

Worsening of motor features is the second most common reason for hospital admissions among people with PD. These features which increase morbidity in people with PD include uncontrolled motor symptoms, prolonged "off" and frequent freezing, "On" and "Offs", dyskinesias, fluctuations and medication side effects. This supports the reports of a systematic review which identified acute deterioration of motor symptoms as the second main cause of admission among people with PD (Koay L et al., 2018). Again, cautious titration of medications in out-patient clinics may prevent a deterioration of motor complications leading to hospital admissions.

2.6.2.3 Falls/fracture-related hospitalisation

The third most common reason for hospital admission among people with PD were falls and fractures. These have been previously recognised as the main reasons for hospital admission in PD. They have also been reported to be a major cause of morbidity, reduced quality of life and increased mortality (Schrag A et al., 2002, Arasalingam A and Clarke CE, 2014).

Falls as a cause of admission is reported to be higher in people with PD than the general older population (Lubomski M et al., 2014). These are a consequence of postural instability, gait abnormalities and postural hypotension. In addition, falls may result as a complication of UTI and motor deterioration in people with PD (Schrag A et al., 2002). Consequently, early assessment and prompt intervention by hospital or community physiotherapists who are trained in PD may lead to a reduction in falls and subsequent fractures among people

with PD (Munneke M et al., 2010, Tomlinson CL et al., 2012, Arasalingam A and Clarke CE, 2014).

2.6.2.4 Cardiovascular-related admissions

The fourth most common reason for hospital admissions among people with PD are cardiovascular comorbidities such as acute coronary syndrome/myocardial infarction and heart failure. Although cardiovascular risk factors are common in the general population and in PD aged group, they have been reported to be increased in PD (Pressley JC et al., 2003, Guttman M et al., 2004). Only two out of the nine included studies had a control group to allow for comparison of excess risk in people with PD (Lubomski M et al., 2014, Braga M et al., 2014). In these cohorts, after comparing age and sex matched controls, cardiovascular disorders were reported to be less represented among people with PD (Lubomski M et al., 2014, Braga M et al., 2014).

2.6.2.5 Neuropsychiatric-related admissions

Neuropsychiatric features were the fifth common reason for hospital admissions among people with PD. These are common non-motor features of PD such as delusions, hallucinations and depression which can be regarded as part of the PD spectrum. It is therefore important to exercise caution in prescribing medications such as those with anticholinergic properties that can precipitate such neuropsychiatric complications (Guttman M et al., 2004, Martignoni E et al., 2004, Klein C et al., 2009, Braga M et al., 2014).

2.6.2.6 GIT-related hospitalisation

The last category of reasons for hospital admissions among people with PD are gastrointestinal problems. These include constipation, dysphagia, nausea and vomiting. People with PD are more likely to require hospital admissions for treatment of GIT problems compared with a control group weighted for age and gender distribution (Lubomski M et al., 2014). These patients require regular monitoring in order to identify and promptly treat the GIT complications. In addition, swallowing assessment, changes to dietary consistency, early recognition and prompt treatment of constipation may help prevent these complications and unwanted admissions (Koay L et al., 2018).

With disease progression, gastrointestinal complications, trauma/falls, infections, electrolyte and genitourinary problems have been reported as indirect reasons for admission which become more troublesome (Paul BS et al., 2017). In addition, the rate of complications due to advancing disease as well as hospital admissions also increases as life expectancy of people with PD increases (Paul BS et al., 2017). It is therefore important to develop pathways for early recognition of all identified reasons for hospital admissions in PD and provide easy access to appropriate care either in the hospital or community. These may lead to significant reduction of unwanted hospitalisation among people with PD.

2.7 Limitations of review methodology

The main limitation of this review's results is in the low number of high-quality studies identified and only two studies had a comparator group without PD.

Another limitation is that only one reviewer screened title and abstract. This process should be carried by two people ideally, but this process was done twice in order to reduce selection bias. Also, data included were largely descriptive resulting in lack of evidence for causal or temporal inferences, however, it was useful for exploring the reasons for admission among people with PD.

Several studies had to be excluded from the meta-analysis as they did not report exact number of people with PD in their cohort and the number admitted for the admission reason given. Reported categorisation of reasons for admission in PD was used in this review and there may be inaccuracies in this.

2.8 Impact of the results on my other studies in the PhD programme

Findings from this review identified gaps in data with regards to rate of hospital admission among people with PD compared with the general population in the UK. Such additional data if available will help in the development of policies and clinical trials to focus on effective preventive strategies addressing the identified reasons for admissions, thereby reducing hospital admissions among people with PD. This may in turn lead to a reduction in mortality, cost to the patients, care givers, health system and the society.

In addition, the review highlighted that most included studies were retrospective and have resulted in underrepresentation of some reasons associated with hospitalisation in PD. This supports my plan to investigate a range of reasons for hospital admissions in PD using prospectively collected data in large UK primary care database-The Health Improvement Network. In Chapter 6, I will

explore hospitalisation in PD: provide an estimate for rate of hospital admissions and reasons for admissions among people with PD in the UK.

2.9 Context of this chapter in overall research work

The results of this review suggest that reasons for hospital admissions among people with PD are varied across studies. However, the main reasons identified include: infections, worsening motor features of PD, falls/fracture, cardiovascular comorbidities and neuropsychiatric problems. It is likely that these reasons are also among the main causes of death for people with PD.

Considering most included studies are retrospective, reasons for hospital admission may have been underreported due to missing information (most studies did not report number of people with PD and the exact number admitted for specific reasons and were excluded, and the possibility of inaccurate categorisation of reported reasons for admission). In the overall plan for the PhD, this review therefore supports the plan to use routinely collected prospective data to explore hospitalisation among people with PD and underlying reasons for hospitalisation.

Chapter 3 The data source for cohort studies: a primary care database- "The Health Improvement Network"

3.1 Chapter overview

In this chapter, I present a summary of electronic medical records and their application in observational studies. I also present a brief description of the main primary care electronic medical records databases in the UK. These include The Health Improvement Network (THIN) which was the source of data for this study.

3.2 Electronic Medical Records (EMR)

3.2.1 Historical background/introduction

The discovery of electronic records in general practice dates back to the year 1970 in Exeter when John Preece was the first GP to use a computer during patient consultation (Benson T, 2002). Thereafter, in 1972, the Department of Health in Exeter conducted a small pilot which turned out to be the first government-sponsored electronic medical records system (Millman A et al., 1995). The government sponsored another initiative ten years later known as "Micros for GP" which involved 150 UK general practices (Millman A et al., 1995). This laid a foundation for more innovations (Benson T, 2002). Following this initiative, two private companies offered computer systems for free to many general practices with the intention to offer anonymised data to pharmaceutical companies in order to recover their initial investment (Benson T, 2002). These strategies which were well known to GPs together with changes in renumeration led to the rapid growth in the number of GP practices using

electronic systems (Millman A et al., 1995). The use of computerized systems has since increased from <5% in the early 1980s to 96% of general practices using electronic records by 1996 (Benson T, 2002) and now a computerised computer system is used for recording of consultations by almost every general practice. This has led to the rich source of patient healthcare data covering many years, which can be used for research (Bradley SH et al., 2018).

3.2.2 Functions of the electronic medical records

In recent years, the use of electronic medical records has become very popular in primary care. The functions of electronic records are grouped as clinical, administrative and statistical with some overlap of functions. In clinical settings, electronic records have become indispensable memory aides to the clinician. These enable the primary care staff to view details of patients' current and previous medical problems (McMillan B et al., 2018). Discussions of previous visits by individuals are available in the electronic records. Prescribing, patient information leaflets and follow up of patients have become easier, safer and cost-effective as some electronic record systems flag up errors for example allergies to medications prescribed.

In addition, use of electronic records in primary care has made executive tasks easier. Keeping timely records of patients' clinical and demographic data; communications to patients and other subspecialties; and transfer of patients' records between general practices are now computerized processes making it less labour-intensive (McMillan B et al., 2018).

A growing wealth of statistical information is available in computerized primary care records. The collection of such data has since been encouraged by the UK government (Tait I, 1981) and computer systems were designed by enthusiastic GPs to collect epidemiological data and this has continued to date.

3.2.3 Functions of electronic medical records for observational research

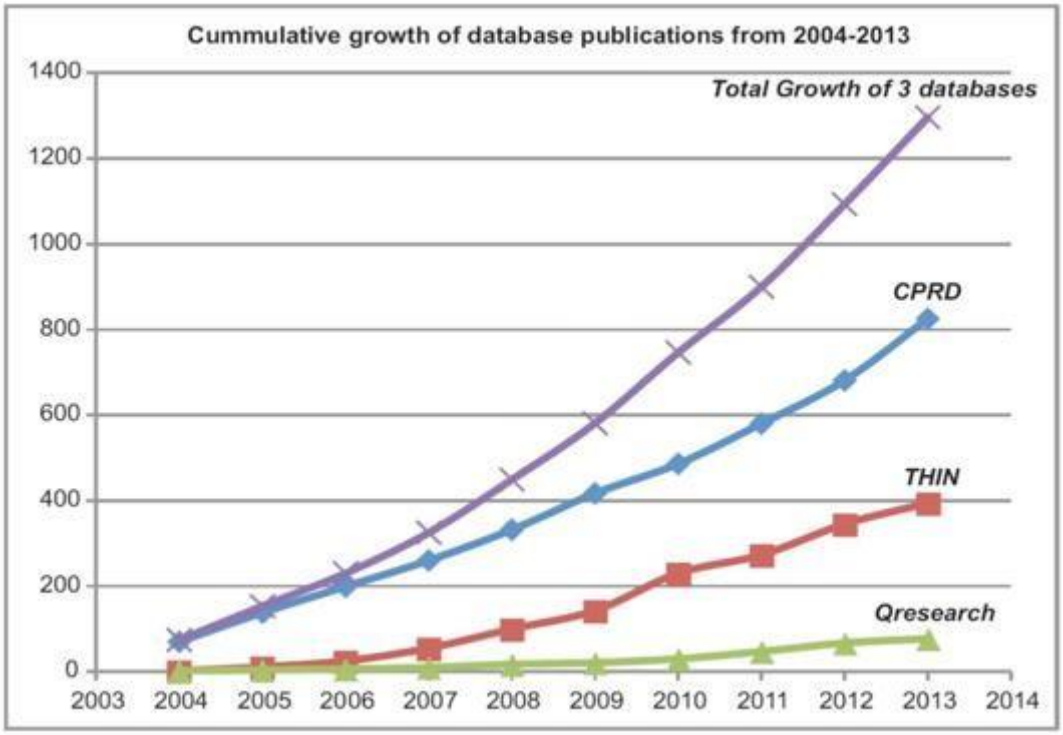
Electronic medical records constitute computerized longitudinal data which are collected and recorded during regular healthcare delivery. In contrast to paper-based patient records, electronic medical records were developed mainly to enhance efficiency and quality of healthcare (Cowie MR et al., 2017). In addition to being used to support clinical workflow (Casey JA et al., 2016), the use of electronic medical records has become popular among researchers in conducting observational and epidemiological research (such as prevalence and incidence studies, health or drug utilization studies, hypothesis generating studies and studies on identification of risk factors); prospective clinical research (such as facilitating patient recruitment and assessing trial feasibility) and safety surveillance and regulatory uses (such as safety investigation of licensed drugs after they have been in the market) (Cowie MR et al., 2017).

Information recorded in electronic medical records vary with clinical needs. Such information covers single aspect of healthcare (for example: primary care, urogenital or accident and emergency medicine) or multiple aspects of healthcare based on the clinical setting (for example: Hospital Episode Statistics, which is database that contains data on all hospitalisations, outpatient appointments and accident & emergency visits at NHS hospitals in England) (NHS Digital, 2019).

3.2.4 Electronic medical records in primary care setting

Overtime, primary care electronic medical record databases have become a rich source of data for research (Petersen I et al., 2019). The explanation for this may be that a high proportion of individuals are registered with a general practice. In June 2017, the number of individuals registered with a general practice in England was estimated to be 58.4 million. During this period, 55.6 million individuals were estimated to be living in England (mid-2017) (NHS Digital, 2020, ONS, 2017). The explanation given for the larger number of individuals registered in a general practice compared to the general population was the inclusion of visitors or individuals who have left the UK and may not be captured by the census. In spite of these explanations, the number of people registered with a general practice in the UK is likely to be high. This, in addition to high proportion of general practices who use computerized systems (almost every GP practice) has made primary care databases, rich source of data for health research in the UK (Protti D et al., 2006, Bradley SH et al., 2018). This is evidenced by the rising annual number of publications using primary care electronic medical record databases (Vezyridis P and Timmons S, 2016, Mannan F et al., 2017) **(Figure 3-1).**

Figure 3-1. Cumulative growth of database research output from 2004 to 2013 (Mannan F et al., 2017).



3.2.5 Electronic medical record databases in the UK

In the UK, there are three main primary care electronic medical record databases which are available for research. These incude:

- **QRESEARCH**: This database contains health records of over 35 million patients registered in 1500 practices which use the EMIS clinical computer system. It is currently domiciled in the University of Oxford (previously at University of Nottingham) and access to the database is given only to researchers employed by UK universities and those on site at the University of Oxford. In addition, access is given only for a subset of the database containing a maximum of 100,000 individuals per

research project approved by the university's scientific review committee (QRESEARCH, 2020).

- **Clinical Practice Research Datalink (CPRD):** This is a large database containing data of 50 million patients from 1800 general practices of which, 14 million are currently registered with a practice. CPRD was formally known as the General Practice Research Database (GPRD). Data from CPRD are split into two databases (CPRD Gold and CPRD Aurum) based on the IT system used by the general practices for patient management. CPRD Gold contains data from practices which use Vision software while CPRD Aurum contains data from practices which use EMIS web software. CPRD is a not-for-profit database owned by the Department of Health and Social Care but license fees for data access are charged to recover cost of research services delivered. The database receives additional funding from the National Institute for Health Research (NIHR) and Medical & Healthcare products Regulatory (CPRD, 2020) (Herrett E et al., 2015).

- **The Health Improvement Network (THIN):** This is one of the largest primary care databases in the UK (Blak BT et al., 2011, Petersen I et al., 2019). It contains data of around 17 million patients who are registered in 700 participating general practices covering about 6% of people living in the UK. THIN was set up in 2002 by IMS Health and In Practice systems in a joint venture. Until 2017, In Practice Systems developed the Vision software, a patient management IT system and IMS Health was involved with managing and providing access to the data. Thereafter, IQVIA acquired the database (IQVIA, 2020). THIN comprises of data which are collected from patients during routine visits to a general practice. These data are regularly updated making data available for analysis up to date (UCL THIN database, 2019). Demographic data, medical information (such as diagnoses, treatment and prescription), additional health information (such as laboratory tests and results) and information on the staff who made the data entry are all available for analysis in THIN. A four-year multi-user and multi-study licence through IQVIA is offered at a departmental level to UCL for a fee (Evan K, 2015).

3.3 My Research in THIN

Students pay licence fees to gain access to use the database for research and get ethical approval once application is reviewed by the Scientific Review Committee. THIN was selected for this research because it has a large number of active patients which are representative of the general UK population. In addition to the database being available in the Department of Primary Care and

Population Health UCL, THIN was chosen for this research as a previous study had demonstrated the feasibility of using this database for PD research (Schrag A et al., 2015).

3.4 Ethics and data permissions

In 2003, the NHS South-east Multi-Centre Research Ethics Committee gave approval for the use of THIN overall. This study was approved by IQVIA Medical Research's Scientific Review Committee in June 2019 (SRC Reference Number: 19THIN034) **(see Appendix 3-1).**

3.5 Recording of data in THIN

In primary care, all information generated are recorded in the database during regular consultations with a general practitioner (GP), nurse or other healthcare staff at a general practice which contributes data to THIN. Such information is then stored across many sets of files generated for each general practice. This information can then be linked between general practices by a patient identifier which is specific and unique to each patient, consultation and healthcare staff. This practice specific unique patient identifier is found in all patient record files (additional health records, medical records, postcode linked information records) **(Figure 3-2).** The following are types of records in THIN:

- **Patient Records**: These contain individual-level information such as: year of birth (for children, month and year of birth are available), sex, date a patient first registered with a general practice, date a patient transferred to a different practice and date a patient died.

- **Medical Records**: These contain details on patient symptoms, diagnoses and secondary referrals which are recorded by a member of staff. The date a stated event occurred (designated as Event date) and the date the record was entered (designated as System date) are available in THIN. Read codes that uniquely identify a specific clinical term are used to code description of symptoms and diagnoses (O'Neil M et al., 1995). Terms that are related are organised into chapters **(Appendix 3-2),** with each chapter being identified by the first character of each code. Read codes are organised in a hierarchical pattern ranging from more general terms to more specific terms. A recording of "Parkinson's disease" for example is assigned the Read code "F12..00" with the "F" indicating it categorised in the Nervous system and sense organ disease chapter and the "12" indicating "Parkinson's disease". Other terms associated with Parkinson's disease such as "Parkinson's disease-NOS" (not otherwise specified) and "Secondary parkinsonism-unspecified" are coded with the Read codes "F12z.00" and "F12X.00" respectively. In order to create a variable for analysis, all related Read codes can be grouped together in a code list. This will be further discussed in subsequent chapters.

- **Therapy Records:** These contain information related to prescription of drugs such as: generic name of the drug, date of prescription, dosage of prescription and quantity of drug prescribed. A unique identifier (drugcode) is given to each medication and a different drugcode is given to each dosage strengths and product forms (for example tablet versus capsule) of the same

medication. In addition, different formulations of the same medication can be identified using BNFcodes as prescriptions are grouped according to the British National Formulary (BNF) classification in THIN (QuintilesIMS, 2017). In this study, therapy records were used to obtain information on patient prescriptions which were used together with Read codes to formulate case definitions used. This is discussed in greater details in subsequent chapters.

- **Postcode Variable Indicator (PVI) Records:** These contain information on Townsend Deprivation quintile which are postcode linked area level indices for socioeconomic status. Information on the ethnicity as a percentage of people living in the area and pollution levels are also recorded in PVI records but were not required for this study.

  In this study, data from PVI records were used to examine the differences in association by socioeconomic status as the Townsend index uses area level information to generate an individual level score. Townsend score is a measure which takes into account car ownership, home ownership, overcrowding in households and unemployment to calculate deprivation at area level (Townsend P et al., 1988). The Townsend score has been divided into quintiles. One is assigned to the least deprived and five (5) to the most deprived. Around 725 of the 744 practices (97%) contributing data to THIN have information on Townsend quintile as not all practices collect data on PVI records.

- **Additional Health Data (AHD) Records**: contain information on personal data that vary with time such as height, weight, blood pressure, smoking status, data on pregnancy; data on vaccinations and reports of

laboratory tests such as cholesterol levels. Although some are better recorded than others, recording of these measurements has markedly improved since the introduction of Quality and Outcomes Framework (QOF) (NHS Employers, 2020); a financial incentives scheme where GPs get compensated depending on quality targets so that they have to record these measurements to meet the set targets. This has led to the regular recording of these measurements (health indicators) in many patients with chronic conditions (Kontopantelis E et al., 2013, Osborn DP et al., 2011), for example regular blood pressure measurement and recording in patients with hypertension.

- **Practice Records**: These contain general practice level information. These include location of the general practice as per region (based on former Strategic Health Authorities) and quality filters which are used to ensure high quality data is available for analysis from each general practice. The quality measures in THIN include: acceptable computer usage date (ACU) and acceptable mortality recording date (AMR). ACU is the date when the general practice reached a level where the computer usage was considered acceptable for recording of patient clinical data and AMR is the date when the general practice reached an acceptable level for mortality recording in the database. In addition, when a general practice is continuously entering on average, at least one medical record, one additional health record (AHD) and two therapy records per patient per year, it is considered to have reached an acceptable level of computer usage and the year is designated the ACU date (Horsfall L et al., 2013). A general practice is considered to have

attained AMR date in the year it reaches expected level of mortality recording similar to that reported from the Office of National Statistics, after accounting for the practice's age/sex structure (Maguire A et al., 2009). Both quality filters serve as a check that general practices have fully migrated from paper-based recording to electronic recording. Around 704 (95%) of the 744 practices contributing data to THIN met the quality assurance criteria.

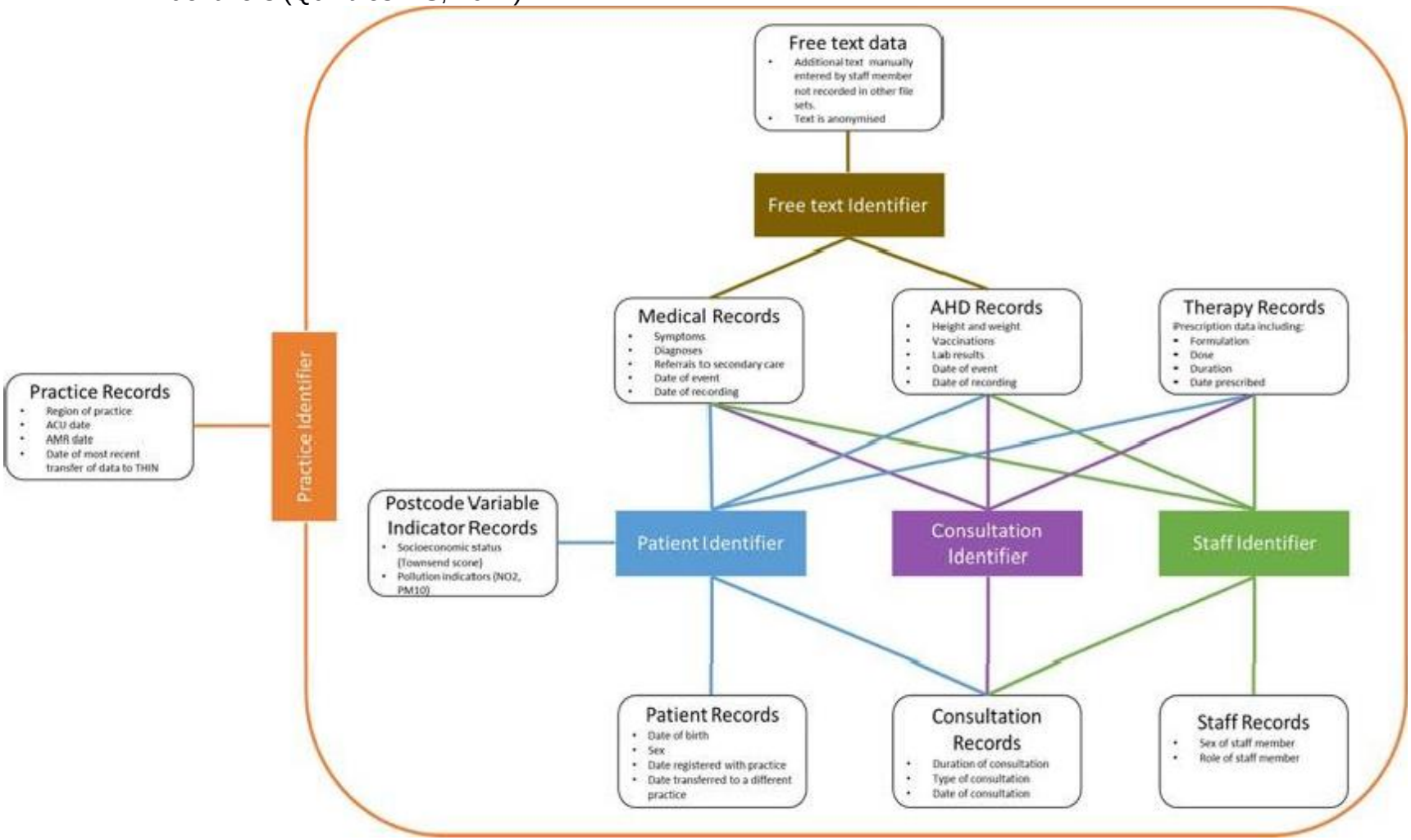
- **Consultation Records:** Information on specific primary care consultations is available in consultation records. Such information recorded include: date of the consultation, length of the consultation and the nature of consultation for example telephone consultation or out-of-hours consultation or surgery-hours consultation. In order to identify multiple recordings in additional health data, medical and therapy records, a unique consultation identifier (consultid) is used to link them to a single consultation thereby identifying all records associated with a single event.

- **Staff Records:** These contain information of all healthcare staff (such as Partner, registrar, nurse, locum etc) in the practice who are involved in entering data in the electronic medical record.

- **Free text records:** Access to these data is restricted because it may include names of individuals and places which are identifiers but still possible with permission and anonymisation after paying a service charge. These records may contain additional information on symptoms,

examinations, diagnoses, differential diagnoses, investigations and information from letters sent from secondary care about disease severity which cannot otherwise be coded (QuintilesIMS, 2017). Free text analysis was not included in my THIN studies due to restrictions.

Figure 3-2. The Health Improvement Network (THIN): Structure of the main data files and their linked identifiers (QuintilesIMS, 2017)



3.6 Strengths and limitations of using THIN for health research

The advantages of using THIN in clinical research are general and specific to individual research: “PD-study” (this study). An advantage is the generalisability of the database. In the UK, the National Health Service requires all individuals, regardless of their health status to be registered with a GP from where most practices contribute data to databases such as THIN. This makes THIN a population-based cohort which is broadly representative of the UK general population with regards to demographics and prevalence of major medical conditions (Blak BT et al., 2011, Lu N et al., 2016). Another advantage is that THIN allows researchers easy and quick access to data since data are automatically recorded when information is entered into the electronic medical record during each consultation. Such data collection is less expensive compared to other study designs in which recruitment of study participants and collection of primary data is required (for example standard cohort studies and clinical trials) (Shephard E et al., 2011).

This study focuses on hospitalisation and mortality which are both outcomes of advanced PD. Much of the available data exploring hospital admissions among people with PD is based on information which was collected retrospectively (as shown in the review: chapter 2 of this thesis). Therefore, using data in THIN which are recorded prospectively, can lead to a reduction in the effect of bias (for example recall bias) linked to retrospective study designs. Also, the continuous nature of the recording of healthcare data can allow longitudinal analysis of hospitalisation and mortality in PD (Chapters 5 and 6). Furthermore, the size of the database makes it ideal to explore hospitalisation and mortality

in PD. Additionally, the database is likely to provide a good representation of PD in UK primary care and the diagnosis of PD is likely to be without recall or selection bias since data are collected prospectively (Schrag A et al., 2015). Also, prescribing data is very accurate and complete, including most long-term PD drugs which are prescribed by GPs. Moreover, regional variations in the diagnosis and management of PD can be explored since practices contributing data to the database are spread throughout the UK.

The use of THIN for research does not come without limitations. One limitation is that the validity of the data is dependent on the quality of information entered into the electronic medical records. These data are captured during routine consultations in the general practice. Some of these data are not recorded at every visit to the GP practice because they may not be directly related to the reason for the current consultation resulting in missing data which is the main challenge with THIN. This sometimes raises significant problems for statistical analysis and interpretation (Marston L et al., 2010, Bhaskaran K et al., 2013). Several methods are therefore used to handle challenges of missing data in THIN. These include complete record analysis which involves the use of only individuals with complete data on variables required for the analysis. In addition, variables with incomplete information could be excluded from the analysis or a separate category for missing values in the incomplete variables could be created. The problems of bias and likely incorrect conclusions that arise from using these approaches are well documented (Greenland S and Finkle WD, 1995, Sterne JAC et al., 2009, O'Kelly M, 2014, Pedersen AB et al., 2017). Also, if a large proportion of individuals do not have the required data, complete record analysis can reduce the sample size resulting in a reduction in the

power of the study (Petersen I et al., 2019). Cautious multiple imputation of missing information has been suggested as a potential approach for resolving the issues of missing data in large primary care databases (Klebanoff MA and Cole SR, 2008, Sterne JAC et al., 2009, Marston L et al., 2010, Kenward MG and Carpenter J, 2016). Another limitation is that data in THIN are captured only from patients who contact or attend primary care, or information is received about them (for example test results, hospital letters, insurance letters or other communications). A further limitation is in the variation of data recording as different practices might record the same information in different ways. For example, different practices may use different Read codes resulting in multiple Read codes within the database for a specific condition. In addition, data that are not captured in THIN are not available for research (Shephard E et al., 2011). For example, non-compliance to medication may constitute a challenge in exploring drug-related exposure since data related to treatment are derived from prescriptions issued (Beardon PH et al., 1993). In addition, drugs prescribed in secondary care or over the counter are not included in THIN. Also, while the contacts in primary care are generally well recorded, there are no reports on how complete these hospital records are. Although, hospital contacts are recorded on the system (for example accident and emergency visits, outpatient letters and admissions), they rely on practices receiving notification and the data being entered resulting in missing data. Lastly, about 24% of the individuals registered in a practice contributing data to THIN were recorded in the least deprived quintile, while 15% were recorded in the most deprived quintile resulting in a slight over-representation of individuals from more affluent areas. Also, individuals registered in THIN are thought to be

slightly older (Blak BT et al., 2011). Nevertheless, the overall representativeness of the database is not thought to be compromised by these minor demographic disparities. THIN is still largely regarded as being representative of national primary care trends and practice by studies using the database (Blak BT et al., 2011, Kneale D et al., 2016).

3.7 Reporting guidelines for observational studies using routine data

The guidelines described in the "REporting of studies Conducted using Observational Routinely collected Data" (RECORD) statement were followed in preparing and reporting the chapters (studies) where THIN was used as the data source (chapters 4, 5 and 6) (Benchimol EI et al., 2015). The RECORD statement is a routinely collected data extension of the "STrengthening the Reporting of Observational studies in Epidemiology" (STROBE) statement. This was developed to enhance the quality of reporting of observational studies (von Elm E et al., 2008). A RECORD statement checklist of where items are reported in this thesis is provided in **Appendix 3-3**.

3.8 Context of this chapter in overall research work

In this chapter, I have reported an overview of electronic medical records and electronic health records databases including THIN. I have also given a description of how data are recorded in the database. I have also provided a summary of the justification for using THIN as the source of data for the subsequent chapters in this thesis. I also describe further study specific strengths and limitations of this data in the relevant chapters.

In the following chapter, I will use individuals identified in THIN as having PD to estimate the incidence of PD in the UK.

Chapter 4 Incidence of Parkinson's disease diagnosis between 2006 and 2016: Analysis of a large UK Primary care database.

4.1 Chapter overview

In this chapter, I present a description of the algorithm used for the extraction of the cohort of individuals with a recording of Parkinson's disease (PD) in THIN. I also show the steps in exploring the trends in the number of incident cases of PD identified over time using four case definitions. Initially, I describe the general steps in investigating incidence of PD and also present the methodology, results, discussion and limitations of the study. A paper titled "Change in the Incidence of Parkinson's disease: Estimates from a large UK Primary Care database" based on these findings has been submitted to Nature Parkinson's disease Journal and is under review.

4.2 Introduction

Over the last 20 to 30 years, there have been reports of changing epidemiological trends of most neurological diseases particularly PD (Rocca WA, 2017, Rocca WA, 2018). The prevalence of PD has increased worldwide (Rocca WA, 2017, Rocca WA, 2018). Whilst the incidence of PD in some studies in Western Europe and North America is reported to have increased, the risk of dementia and stroke is reported to have declined (Rocca WA, 2017, Rocca WA, 2018). However, there are few incidence studies that assess the same population at different time points with similar case ascertainment methods due to difficulties in identifying people with PD in a stable and generalisable population over time (Park JH et al., 2019). Most studies are

cross-sectional, assess prevalence, and cannot account for changes in diagnostic patterns resulting in varying epidemiological trends in most regions of the world (Wang S-J et al., 1996, Kuopio AM et al., 1999, Chen R et al., 2001, Chen CC et al., 2009, Rocca WA, 2017, Rocca WA, 2018). Amongst incidence studies, some report an increase (Savica R et al., 2016, Isotalo J et al., 2017, Park JH et al., 2019) whereas others show no change (Akushevich I et al., 2013) or a decrease in incidence of PD over time (Horsfall L et al., 2013, Darweesh SK et al., 2016, Liu WM et al., 2016). Some of these studies were limited by sample size (Darweesh SK et al., 2016, Savica R et al., 2016) and so were unable to provide stable incidence rates or conduct a definitive age-standardised cohort analysis over time (Savica R et al., 2016). Others were retrospective studies and limited by inadequate case ascertainment (Liu WM et al., 2016) and one prospective study had small follow-up time (Park JH et al., 2019). Also, very few studies have assessed temporal trends in the incidence of PD in the UK (Horsfall L et al., 2013). There are no available studies which have explored the effect of different case definitions on the incidence of PD.

The use of electronic medical records with appropriate case ascertainment allows for a consistent method of exploring trends in PD diagnosis over time as they are a rich source of clinical and demographic data. Electronic medical records remain popular in observational research (discussed in detail in chapter 3) and have been used in several studies for investigating trends in the incidence of conditions over time (Shallcross LJ et al., 2015, Sharma M et al., 2016, Basatemur E et al., 2017, Cowie MR et al., 2017). The issue of underreporting due to selection bias is mitigated as data are collected routinely at the time of recording a PD diagnosis in the database. This diagnosis is

based on codes which are entered following letters received from the hospital specialist confirming the diagnosis. This is commonly checked by the General Practitioner (GP) who flags it for data entry by the administrative staff. The validity of significant diagnoses in primary care databases is high (Lewis JD et al., 2007, Langley TE et al., 2010) and that of PD using diagnosis Read codes and at least two prescriptions of antiparkinsonian medications is also high. In a previous study, 90% of PD diagnoses (using diagnosis code and at least two prescriptions of antiparkinsonian medication) in General Practice Research Database (GPRD), a similar primary care database to THIN, were validated as true cases when compared to paper records from a random sample of patients (Alonso A et al., 2007). In addition, significant diagnoses of long-term conditions have good specificity and sensitivity in primary care records (Khan NF et al., 2010, Herrett E et al., 2011). The limitations in terms of diagnostic accuracy can be partly mitigated and explored by using different case definitions of varying stringency. In order to identify changes in incidence of PD in the UK, I examined incidence rates of PD in THIN, using the same ascertainment methods over time, employing several definitions (defined using diagnosis Read codes and symptom Read codes alone or in combination and in combination with drug codes) **(see Section 4.4.4)** to account for changes in diagnostic patterns over time.

My aim was to use four case definitions to investigate changes in the incidence of PD between 2006 and 2016 and to explore the effect of age, gender, social deprivation and regional location of practices on the incidence of PD using THIN.

4.3 Study objectives

- To estimate the incidence of PD in THIN using four different case definitions generated from combination of diagnosis Read code, symptom Read code and treatment code (drug code).
- To investigate the changes in incidence of PD between 2006 and 2016 in UK primary care.
- To investigate the association between age, gender, social deprivation, general practice location (in terms of region) and incidence of PD in UK primary care.

4.4 Methods

4.4.1 Data source

The Health Improvement Network, a primary care database **(See Chapter 3).**

4.4.2 Study population

General practices that contributed data to THIN between January 2006 and December 2016 were used for this study. The quality of the data included was assessed using two quality filters: acceptable computer usage (ACU) dates which is used to determine when a general practice was using electronic recording fully (Horsfall L et al., 2013) and the acceptable mortality recording (AMR) date. AMR date is a measure of the quality of death records in THIN (Maguire A et al., 2009) **(See Chapter 3, section 3.5).** Practices were included after the latest of the ACU and AMR dates. Of 744 practices at the time of the study, seventeen practices did not have any information on postcode linked

socioeconomic indices (Townsend quintile) and were excluded from the analysis.

4.4.3 Study participants

All individuals aged 50 years and over who were registered with a general practice contributing data to THIN between January 1st, 2006 and December 31st, 2016 were included in the analysis.

4.4.4 Identification of Parkinson's disease cases in THIN

Parkinson's disease diagnosis in primary care was defined by Read classification (Chisholm J, 1990). PD cases were identified using diagnosis Read codes or a combination of diagnosis and symptom Read codes or combination of diagnosis Read codes, symptom Read codes and treatment codes (drug codes) **(See Figure 4-1).** Four case definitions **(See Figure 4-2)** were developed to identify individuals with a diagnosis of PD in THIN:

1. A PD diagnosis Read code and at least two antiparkinsonian drug prescriptions from 5 classes. This method of case ascertainment of PD has been validated in General Practice Research Database (GPRD), another primary health care database (Alonso A et al., 2007) and used in a previous study in THIN by three of my supervisors (Schrag A et al., 2015). This is the strictest definition (most specific) and was used to identify incident cases which were used for subsequent cohort studies described later in this thesis.
2. A PD diagnosis Read code alone.

3. A PD diagnosis Read code OR Read code for parkinsonian symptom, secondary and unspecified parkinsonism (excluding drug-induced parkinsonism).
4. A PD diagnosis Read code OR symptom Read code OR at least one antiparkinsonian drug prescription from 5 classes of antiparkinsonian medication. This is the broadest and most inclusive (sensitive) case definition.

Each case definition is based on individuals having the following records:

- **A diagnosis Read code for Parkinson's disease:**

  A Read code list indicating a diagnosis of PD was developed **(See Appendix 4-1a).** Individuals were considered to have a diagnosis of PD if they had a diagnosis Read code within their medical records. The earliest record of PD diagnosis Read code is considered the index date of diagnosis for incident cases.

- **A symptomatic Read code for Parkinson's disease diagnosis:**

  A symptom Read code list was developed **(See Appendix 4-1b).** Individuals were considered potential cases of PD if they had a symptom Read code for PD within their medical records. This was used in combination with a diagnosis Read code to define PD cases. The earliest record of PD diagnosis Read code is considered the index date of diagnosis for incident cases.

- **A prescription for antiparkinsonian medication:**

  Antiparkinsonian drug prescriptions except for anticholinergics were used. These medications are almost exclusively used in Parkinsonism except in younger patients where they are used for some endocrine disorders. However, pramipexole, rotigotine and ropinirole use was extended to restless leg syndrome in 2006/2007 and patients with restless leg syndrome were excluded except if they also had a diagnosis code for PD. Drug code lists for these antiparkinsonian medications were developed **(See Appendix 4-1c).** The earliest date of the antiparkinsonian prescription was considered the index date of diagnosis for incident cases. These were used in combination with PD diagnosis Read code and symptom Read code **(See Figure 4-2)** to form the four case definitions.

Read code and drug code lists **(See Appendix 4-1a to Appendix 4-1c)** used for the extraction of PD cases for analysis were generated through previously developed methods (Dave S and Petersen I, 2009). These Read codes and drug codes were then applied to the medical records and therapy records of individuals (depending on case definition) in THIN to identify the desired cohort.

Figure 4-1. Read codes used for case identification.

PD diagnosis Read codes

Read code	Description	Type
Eu02300	[X]Dementia in Parkinson's disease	diagnosis
F11x900	Cerebral degeneration in Parkinson's disease	diagnosis
F12..00	Parkinson's disease	diagnosis
F12z.00	Parkinson's disease NOS	diagnosis
F130300	Parkinsonism with orthostatic hypotension	diagnosis

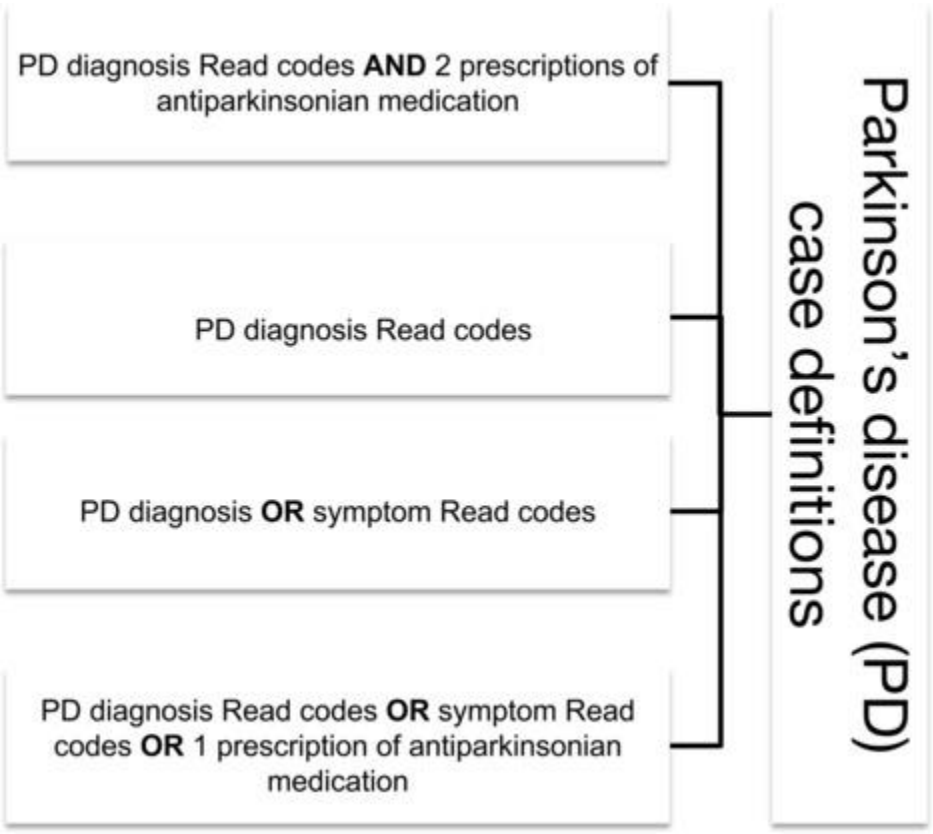
PD diagnosis Read codes and symptom Read codes

Read code	Description	Type
2944.00	O/E - muscle rigid - cogwheel	symptom
2944.11	O/E - cog wheel rigidity	symptom
297A.00	O/E - Parkinsonian tremor	symptom
2987.00	O/E -Parkinson flexion posture	symptom
2987.11	O/E - Parkinson posture	symptom
2994.00	O/E-festination-Parkinson gait	symptom
2994.11	O/E - Parkinson gait	symptom
A94y100	Syphilitic parkinsonism	diagnosis
Eu02300	[X]Dementia in Parkinson's disease	diagnosis
F11x900	Cerebral degeneration in Parkinson's disease	diagnosis
F12..00	Parkinson's disease	diagnosis
F123.00	Postencephalitic parkinsonism	diagnosis
F12X.00	Secondary parkinsonism, unspecified	diagnosis
F12z.00	Parkinson's disease NOS	diagnosis
F130300	Parkinsonism with orthostatic hypotension	diagnosis
F13z300	Akinetic rigid syndrome	diagnosis
Fyu2100	[X]Other secondary parkinsonism	diagnosis
Fyu2200	[X]Parkinsonism in diseases classified elsewhere	diagnosis
Fyu2900	[X]Secondary parkinsonism, unspecified	diagnosis

5 classes of antiparkinsonian medications:

Levodopa-containing medications
Dopamine-receptor agonists
Amantadine
Monoamine oxidase-B inhibitors-MAOB-I (rasagiline and selegiline hydrochloride)
Catechol-O-methyl transferase inhibitors-COMT-I (entacapone and tolcapone)

Figure 4-2. Four case definitions using PD diagnosis Read codes, Symptom Read codes and treatment codes (drug codes).



4.5 Identification and reducing sources of misclassification bias in the identification of Parkinson's disease cases

In order to ensure good quality data output, all general practices contributing data to THIN receive adequate training on recording of data (QuintilesIMS, 2017). In spite of this, when using routinely collected electronic data, cases could be misclassified due to the potential for recording error at the time of data entry (Manuel D. G. et al., 2010). Such misclassification in the absence of confirmatory tests, may have effects on results leading to misrepresentation of cases.

The results of using the case definitions (algorithms) described were compared with a previous similar study (Horsfall L et al., 2013) to identify any deviations.

In order to detect, diagnose and edit any data abnormalities during the process of identifying PD cases in THIN, I used the data cleaning framework described by Van den Broeck et al (Van den Broeck J et al., 2005) which involves a three-stage process of :

1. **Screening phase:**

   This process involves screening for dearth or excess data; deviations; bizarre patterns and unexpected results of analysis done.

2. **Diagnostic phase**

   This stage involves clarifications as to whether the suspected data abnormality is correct or an error.

3. **Editing phase**

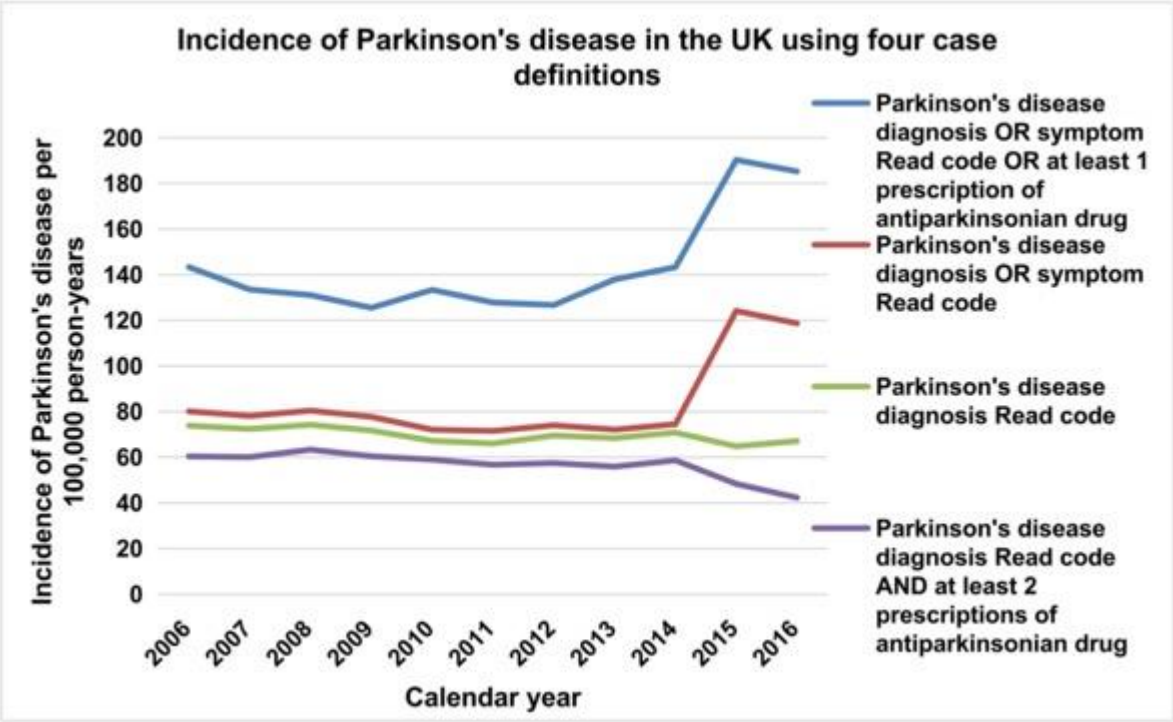
   This last stage involves making a decision on how to proceed with any identified data abnormalities. Such decisions include: correcting the error, deleting the observations or leaving the data untouched. At this stage, the results are rescreened after correcting or deleting the observation, to assess whether the irregularities in the data has been resolved.

4.5.1 Screening phase:

To screen for irregularities in my data, the four case definitions **(See Section 4.4.4)** were run, and line graphs were used to explore the incidence of PD per year **(See Figure 4-3).** I expected a gradual decline in incidence over time similar to a previous study (Horsfall L et al., 2013) but there was an unexpected sharp rise in incidence in 2015 and sudden decline in 2016 using the third case definition (PD diagnosis Read code **OR** symptom Read code) and fourth case

definition (PD diagnosis Read code **OR** symptom Read code **OR** at least one prescription) **(See Section 4.4.4).** This needed to be further explored.

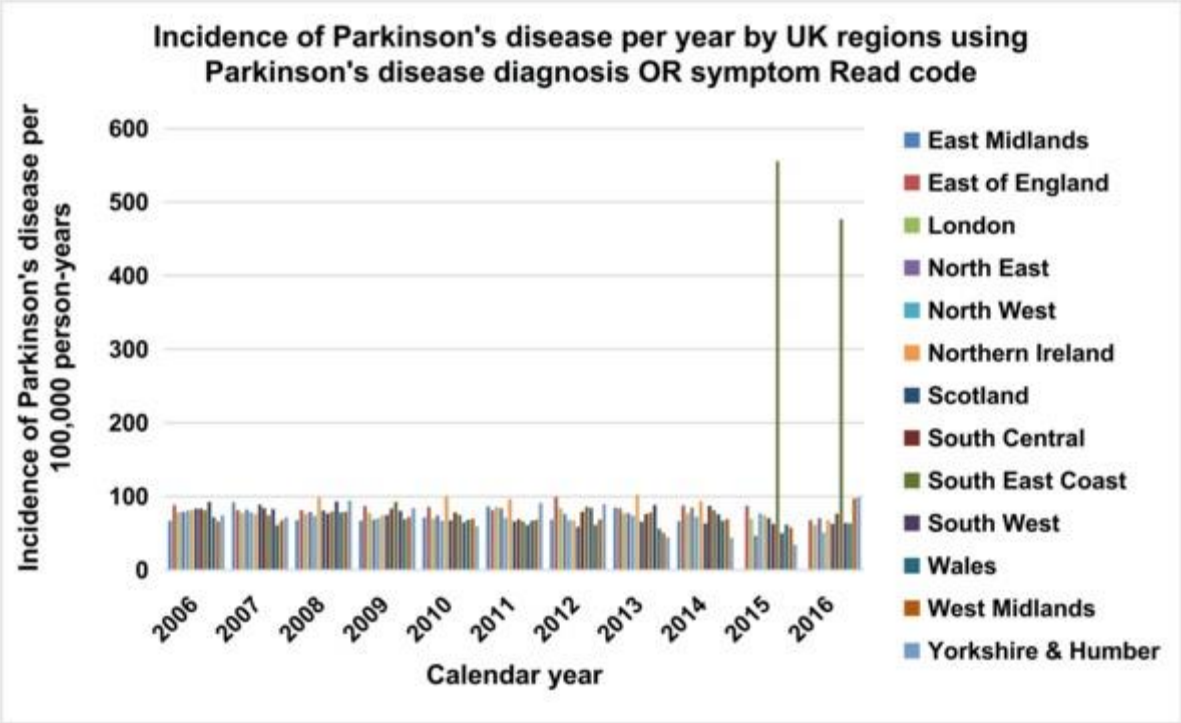
Figure 4-3. Graphs showing incidence of Parkinson's disease in UK using four case definitions (with abnormal records).



I then used histograms for further explorations of PD incidence derived from two case definitions ((PD diagnosis Read code **OR** symptom Read code) and (PD diagnosis Read code **OR** symptom Read code **OR** at least one prescription)) that showed irregular graphs. Initially, I examined the incidence of PD per UK region per year and incidence of PD per general practice per year. This showed that one general practice in the South East Coast region recorded excessively higher number of PD cases using a particular symptom Read code in 2015 and 2016 compared to other practices in the region. The entries were done by different staff at the practice and there was no information suggesting the reason for such abnormal entries. This was found to be the explanation for

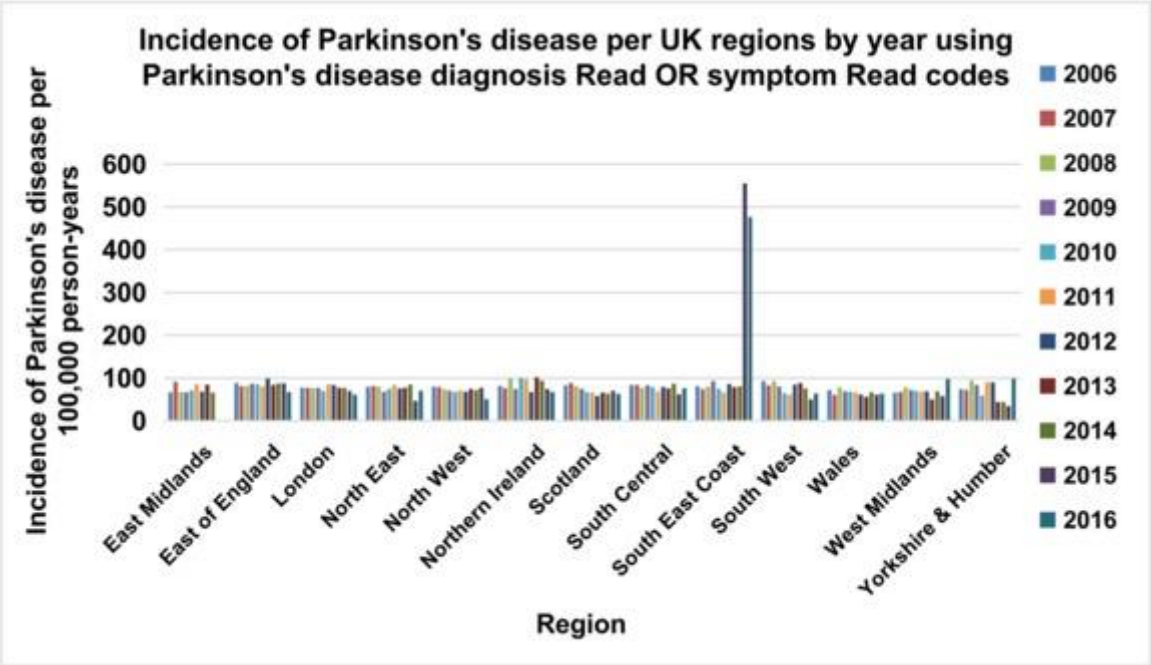
the unexpected sharp rise in incidence of PD using the third (diagnosis Read code **OR** symptom Read code) and fourth (diagnosis Read code **OR** symptom Read code **OR** at least one prescription of antiparkinsonian medication) case definitions **(See Figures 4-4, 4-5 and 4-6 and Appendix 4-2a: Figures 4-1 and 4-2).**

Figure 4-4. Graph showing incidence of Parkinson's disease per year by UK region using Parkinson's disease diagnosis Read code OR symptom Read code (with abnormal records).



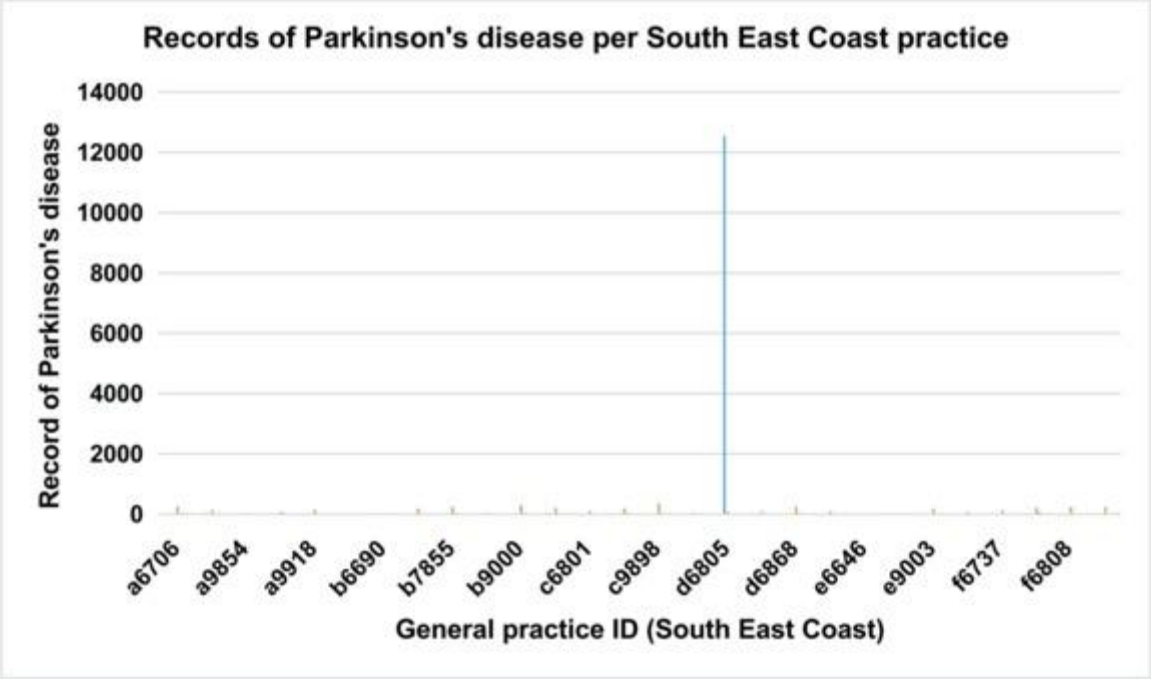
South East Coast practice showed abnormal recording of PD in 2015 and 2016

Figure 4-5. Graph showing incidence of Parkinson's disease per UK region by year using Parkinson's disease diagnosis OR symptom Read (with abnormal records).



In the years 2015 and 2016, a South East Coast practice showed abnormal recording of PD

Figure 4-6. A graph showing records of Parkinson's disease cases per South East Coast general practice (with abnormal records).



Practice number d6805 had abnormally high records of PD.

4.5.2 Diagnostic phase:

The full electronic medical records of the identified cases in the South East Coast practice with excessively large number of PD records was probed. This showed, in comparison to the PD diagnosis Read code, that this practice entered a particular non-specific symptom code ("F13z300") designated for "Akinetic Rigid syndrome" for PD recording. The exact reason why this happened could not be ascertained from available records.

4.5.3 Editing phase

In order to reduce the effect of miscoding (ie the diagnosis of PD coded for a symptom Read code), the South East Coast practice ("d6805") which used symptom code for "Akinetic Rigid Syndrome" ("F13z300") was excluded across all case definitions. Following the application of this exclusion criteria, the sharp rise in incidence of PD seen with the third and fourth case definitions normalised and was comparable to the previous similar study in THIN **(See Figure 4-7 to 4-10 and Appendix 4-2b: Figures 4-3 and 4-4).**

Figure 4-7. Graphs showing incidence of Parkinson's disease in UK using four case definitions after excluding the practice with disproportionately large recording of Parkinson's disease symptom Read code.

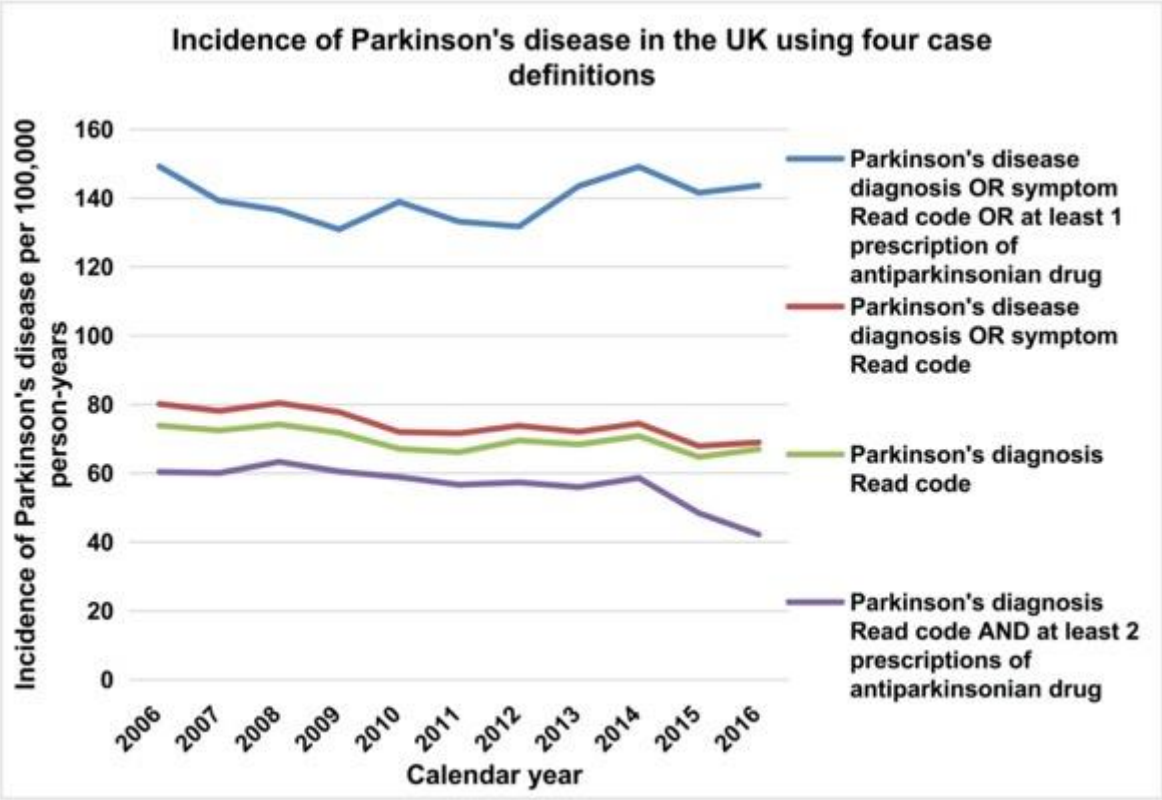


Figure 4-8. Graph showing incidence of Parkinson's disease per year by UK region using Parkinson's disease diagnosis OR symptom Read code after excluding the practice with disproportionately large recording of Parkinson's disease.

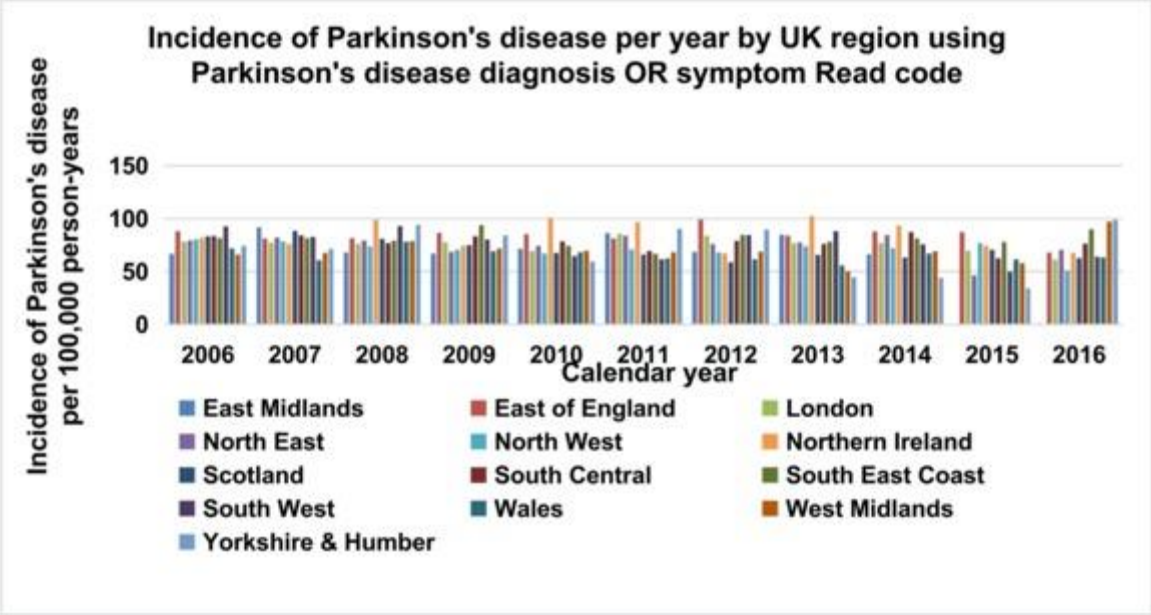


Figure 4-9. Graph showing incidence of Parkinson's disease per UK region by year using Parkinson's disease diagnosis OR symptom Read code after excluding the practice with disproportionately large recording of Parkinson's disease.

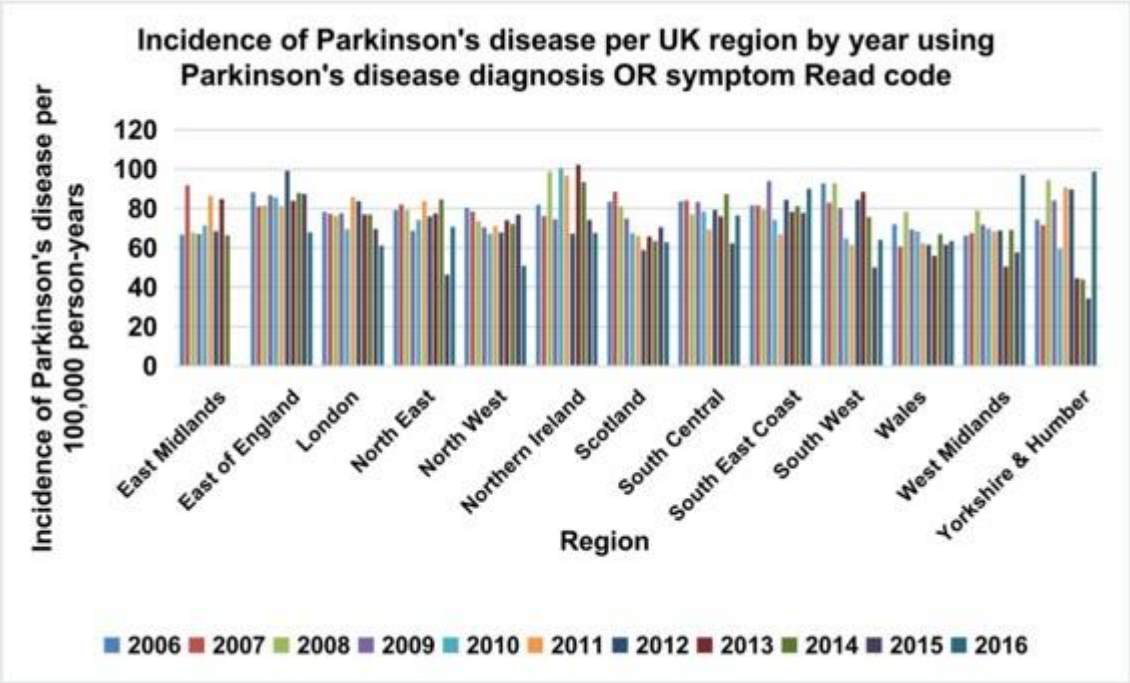
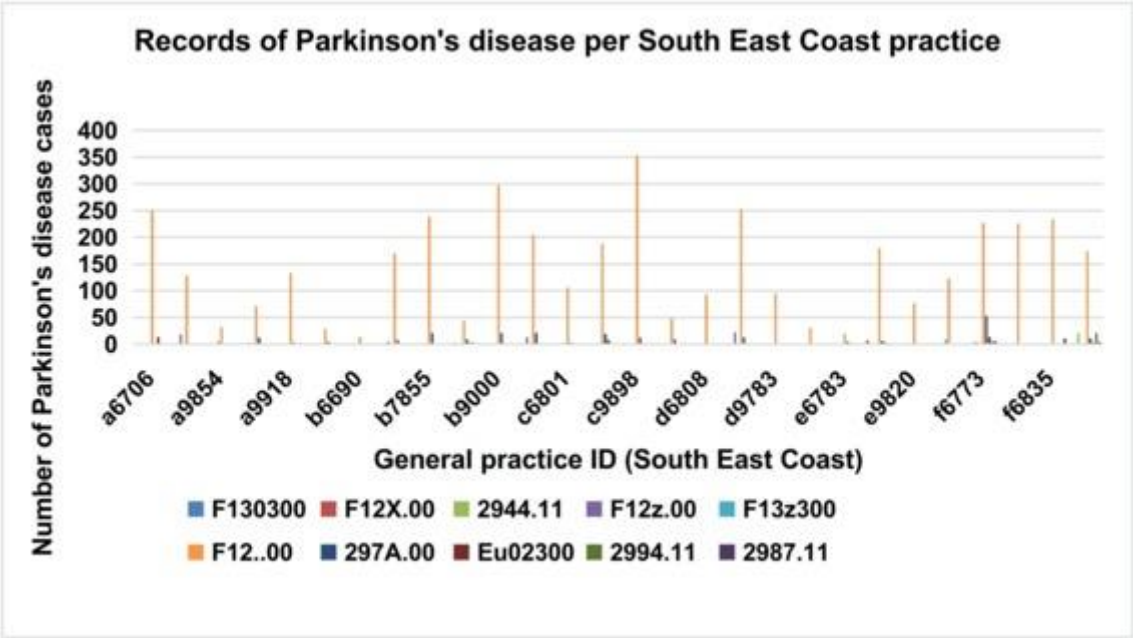


Figure 4-10. A graph showing records of Parkinson's disease cases per South East Coast general practice per Read code after excluding the practice with disproportionately large recording of Parkinson's disease symptom Read code.



F13z300 was the code used in the practice d6805 which was excluded.

4.6 Incidence of Parkinson's disease

The use of the term incidence in this study with regards to PD refers to the first recorded entry of PD in the patient's electronic medical records**.**

4.7 Analysis

The overall crude incidence of PD recording using all four case definitions was estimated as the number of cases per 100,000 Person Years At Risk (PYAR). In primary care records, incidence rates could be overestimated if the follow-up time used is shortly after patient's registration with a General Practitioner. This is because when a patient registers with a new practice they usually provide a list of their ongoing (ie prevalent) health conditions, and these can be entered with the data of registration instead of the true date of onset. Therefore, in order to measure incidence rates accurately, this follow-up time which differs according to diseases, must be excluded (Lewis JD et al., 2005). For this study, the first record of diagnosis or symptom or prescription date had to be at least six months following the patient's registration with a GP practice for all incident cases. This time period has been used in previous studies, as newly recorded cases at registration with a new GP can commonly erroneously include prevalent cases (Lewis JD et al., 2005).

This incidence of PD was calculated by adding the total number of patients with a first recording of diagnosis or symptom or prescription plus six months, between 2006 and 2016 and this number was then divided by the total person years of follow-up for all patient records for this time period. The start date

used to calculate the total person years at risk for each study participant was the latest of:

- The start date of the study period: January 1st, 2006.
- The date the individual registered with their current general practice plus six months.
- The date the practice reached acceptable mortality rate (AMR).
- The date the practice reached acceptable computer usage (ACU).

The end date used was the earliest of:

- The study end date: December 31st, 2016.
- The date the individual transferred to another practice.
- The date of death recorded in the practice.
- The last date the practice contributed data to THIN.
- The date of diagnosis (index date of diagnosis) for individuals with PD.

The crude incidence rates of PD recording using all four case definitions were estimated by age group, gender, social deprivation, calendar year and region, restricting the person years of follow-up according to the category in question. For descriptive analysis, age group was defined by 5-year intervals: 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84, 85 to 89, 90 to 94, and 95 years and over. Gender was defined as male and female. Townsend quintile was used to assess the level of social deprivation (**See Chapter 3, Section 3.4**). The UK regions were based on the former Strategic Health Authorities. These were: East Midlands, East of England, London, North East, North West, Northern Ireland, Scotland, South Central, South East Coast, South West, Wales, West Midlands, Yorkshire and Humber.

Multivariable Poisson regression analysis was conducted to investigate the incidence (using the four case definitions) by age group, gender, Townsend quintile, calendar year and region; adjusting for the respective variables included in this model. In order to fit the Poisson model to generate a rate ratio, the coefficients were exponentiated with person-time specified as the exposure.

Using all four case definitions, annual incidence rates were calculated in order to explore trends in the incidence of PD recordings over time. This was calculated between 2006 and 2016 by: 10-year age band (50 to 59 years, 60 to 69 years, 70 to 79 years, 80 to 89 years and 90 years and over; gender (male and female); level of social deprivation (Townsend quintile 1 and 2, Townsend 3, Townsend 4 and 5 and those with missing Townsend data and UK geographic region (England, Northern Ireland, Scotland, Wales).
Stata (version 16MP) was used to carry out all statistical analyses (StataCorp., 2019).

4.8 Further exploratory work in THIN

In order to check my codes, I applied them to the time period of a previously undertaken study in the THIN database using the same codes (**See Appendix 4-3**). I compared the overall incidence rates with my own time period: 2006 and 2016. I also compared my results with the results of a report on the incidence of PD published by Parkinson's UK. In this report, they used only diagnostic Read codes (F12..00 Parkinson's disease, F120.00 Paralysis agitans, F12z.00 Parkinson's disease not otherwise specified) for PD case identification, so I compared these with the same definition from my study. Overall incidence rates

in these studies were similar to mine using similar Read codes. These results are presented in **Appendix 4-3.**

4.9 Ethics and data permissions

See Chapter 3 (section 3.4) and **Appendix 3-1.**

4.10 Results

I am presenting the results for Incidence of PD using two case definitions: the strictest (specific) and the broadest (sensitive) case definitions. For brevity, the results for the other two intermediate case definitions are presented in the **Appendices 4-4 to 4-13.** Overall crude incidence rate of PD both case definitions were 70 per 100,000 PYAR (95%CI: 69 to 71) (PD codes only) and 75 per 100,000 PYAR (95%CI: 73 to 76) (PD codes or symptom codes) and both showed a declining trend between 2006 and 2016.

The strictest case definition was used to identify incident cases which were used for the other cohort studies in this thesis because it is more specific and robust. The broadest case definition allows for comparison with a similar previous study.

4.10.1 Incidence of Parkinson's disease

The overall crude incidence rate of PD between 2006 and 2016 as defined by the strictest case definition was (1) 57 per 100,000 PYAR (95%CI: 56 to 58) using PD diagnosis codes and at least 2 prescriptions of antiparkinsonian medication; and the broadest case definition was (2) 140 per 100,000 PYAR (95% CI: 138 to 141) using PD diagnosis **OR** symptom Read codes **OR** at least

one prescription of antiparkinsonian medication **(Table 4-1 and Table 4-2 Appendix 4-4 and Appendix 4-5: Table 4-3 and Table 4-4).**

Table 4-1. Incidence of Parkinson's disease by age, sex, Townsend quintile, calendar year and region using the strictest (specific) case definition (diagnosis Read codes AND at least 2 prescriptions of any antiparkinsonian medication) *IRR adjusted for age, gender

	Number of cases	Person-years (100,000)	Incidence of PD Rate per 100,000 (95%CI)	Adjusted *IRR (95%CI)
Overall	10,104		57 (56-58)	
Age, years				
50-54	294	33.60	8.75 (7.80-9.81)	(Reference)
55-59	497	30.68	16.20 (14.84-17.69)	1.86 (1.60-2.16)
60-64	892	29.15	30.60 (28.66-32.68)	3.57 (3.11-4.09)
65-69	1,435	25.02	57.36 (54.47-60.40)	6.65 (5.84-7.58)
70-74	1,971	19.90	99.05 (94.77-103.52)	11.62 (10.22-13.20)
75-80	2,220	16.05	138.36 (132.72-144.24)	16.46 (14.50-18.69)
80-84	1,678	11.75	142.85 (136.17-149.85)	17.26 (15.17-19.65)
85-89	874	7.06	123.78 (115.84-132.27)	15.30 (13.33-17.57)
90-94	214	2.88	74.42 (65.09-85.09)	9.77 (8.14-11.73)
95+	29	0.81	35.88 (24.93-51.63)	4.65 (3.11-6.96)
Sex				
Male	6,135	83.83	73.18 (71.34-75.04)	(Reference)
Female	3,969	93.05	42.66 (41.35-44.00)	0.52 (0.50-0.55)
Townsend quintile				
1	2,811	45.36	61.97 (59.72-64.30)	(Reference)
2	2,320	39.87	58.19 (55.87-60.61)	0.91 (0.86-0.97)
3	1,901	34.22	55.55 (53.11-58.10)	0.88 (0.82-0.93)
4	1,441	27.13	53.12 (50.45-55.93)	0.83 (0.78-0.89)
5 (Most deprived)	895	17.28	51.80 (48.52-55.30)	0.82 (0.76-0.89)
Missing	736	13.02	56.53 (52.59-60.76)	
Year				
2006	961	15.91	60.42 (56.72-64.36)	(Reference)
2007	990	16.47	60.12 (56.48-63.97)	0.98 (0.90-1.08)
2008	1,070	16.89	63.36 (59.68-67.27)	1.05 (0.96-1.14)
2009	1,035	17.10	60.54 (56.97-64.35)	0.97 (0.88-1.06)
2010	994	16.87	58.93 (55.38-62.72)	0.94 (0.86-1.03)
2011	975	17.20	56.70 (53.25-60.37)	0.91 (0.83-1.00)
2012	999	17.43	57.32 (53.87-60.98)	0.93 (0.85-1.02)
2013	953	17.02	56.00 (52.55-59.67)	0.90 (0.82-0.98)
2014	949	16.19	58.62 (55.00-62.47)	0.93 (0.85-1.02)
2015	681	14.05	48.46 (44.95-52.23)	0.76 (0.69-0.84)
2016	497	11.77	42.24 (38.69-46.12)	0.67 (0.60-0.75)
Region				
Wales	1,002	20.03	50.02 (47.02-53.22)	(Reference)
East Midlands	197	3.65	53.99 (46.95-62.08)	0.98 (0.82-1.19)
East of England	623	9.60	64.90 (60.00-70.20)	1.22 (1.07-1.39)
London	1,002	17.16	58.40 (54.90-62.13)	1.21 (1.08-1.35)
North East	212	3.62	58.60 (51.22-67.05)	1.17 (0.97-1.41)
North West	918	16.88	54.37 (50.97-58.01)	1.07 (0.95-1.20)
Northern Ireland	500	7.25	69.00 (63.21-75.32)	1.46 (1.28-1.68)
Scotland	1,526	28.95	52.71 (50.13-55.43)	1.15 (1.04-1.27)
South Central	1,121	18.84	59.50 (56.12-63.01)	1.13 (1.01-1.26)
South East Coast	1,194	18.58	64.25 (60.71-68.00)	1.24 (1.11-1.38)
South West	871	14.64	59.50 (55.67-63.58)	1.09 (0.97-1.22)
West Midlands	761	14.32	53.13 (49.49-57.04)	1.01 (0.89-1.14)
Yorkshire & Humber	177	3.36	52.65 (45.44-61.01)	1.02 (0.84-1.25)

***IRR adjusted for age, gender, calendar year, social deprivation and UK regions. CI-Confidence interval.

Table 4-2. Incidence of Parkinson's disease by sociodemographic factors, calendar year and region using broadest (most sensitive) diagnosis Read code OR symptom Read code OR at least 1 prescription of any antiparkinsonian medication. *IRR adjusted for age, gender

	Number of cases	Person-years (100,000)	Incidence of PD Rate per 100,000 (95% CI)	Adjusted *IRR (95% CI)
Overall	24,487		140.00 (138.00-141.00)	
Age, years				
50-54	1,506	33.43	45.04 (42.82-47.38)	1(Reference)
55-59	1,835	30.52	60.13 (57.44-62.94)	1.34 (1.25-1.44)
60-64	2,471	28.97	85.30 (82.01-88.73)	1.91 (1.79-2.05)
65-69	3,234	24.83	130.27 (125.86-134.84)	2.90 (2.72-3.09)
70-74	3,996	19.71	202.72 (196.53-209.11)	4.53(4.26-4.82)
75-80	4,523	15.89	285.03 (276.84-293.46)	6.46 (6.08-6.86)
80-84	3,781	11.60	325.90 (315.68-336.45)	7.40 (6.95-7.87)
85-89	2,308	6.97	331.30 (318.05-345.09)	7.53 (7.03-8.06)
90-94	715	2.84	252.15 (234.33-271.32)	5.81 (5.29-6.38)
95+	118	0.80	147.77 (123.38-176.99)	3.29 (2.69-4.01)
Sex				
Male	12,599	83.14	151.55 (148.92-154.22)	(Reference)
Female	11,888	92.39	128.67 (126.38-131.01)	0.76 (0.74-0.78)
Townsend quintile				
1	6,030	45.0	147.12 (141.49-152.98)	(Reference)
2	5,442	39.6	144.95 (140.47-149.57)	1.07(1.02-1.12)
3	4,642	34.0	137.53 (133.92-141.23)	1.03(0.99-1.07)
4	3,900	26.9	136.70 (132.83-140.69)	0.99 (0.95-1.03)
5 (Most deprived)	2,520	17.1	133.86 (130.52-137.28)	0.98 (0.94-1.02)
Missing	1,953	12.9	151.20 (144.6-158.00)	
Year				
2006	2,357	15.8	149.22 (143.32-155.37)	(Reference)
2007	2,277	16.4	139.20 (133.60-145.04)	0.92 (0.87-0.98)
2008	2,289	16.8	136.51 (131.03-142.22)	0.91 (0.86-0.97)
2009	2,222	17.0	130.92 (125.58-136.47)	0.86 (0.80-0.91)
2010	2,325	16.7	138.88 (133.35-144.64)	0.91 (0.86-0.97)
2011	2,273	17.1	133.19 (127.82-138.78)	0.88 (0.83-0.93)
2012	2,279	17.3	131.77 (126.47-137.30)	0.86 (0.81-0.92)
2013	2,423	16.9	143.53 (137.93-149.46)	0.92 (0.87-0.98)
2014	2,394	16.1	149.13 (143.27-155.23)	0.96 (0.91-1.02)
2015	1,972	13.9	141.56 (135.45-147.95)	0.89 (0.83-0.95)
2016	1,675	11.7	143.66 (136.94-150.71)	0.92 (0.86-0.99)
Region				
North East	420	3.6	116.77 (106.12-128.49)	(Reference)
East Midlands	501	3.6	138.40(126.79-151.06)	1.14 (0.92-1.42)
East of England	1,439	9.5	151.16 (143.55-159.17)	1.25 (1.03-1.51)
London	2,155	17.0	126.50 (121.27-131.96)	1.04 (0.87-1.25)
North West	2,290	16.7	136.81 (131.32-142.53)	1.16 (0.97-1.39)
Northern Ireland	1,235	7.2	172.18 (162.84-182.05)	1.51 (1.25-1.83)
Scotland	4,010	28.7	139.58 (135.33-143.97)	1.22 (1.02-1.44)
South Central	2,462	18.7	131.63 (126.53-136.94)	1.09 (0.91-1.31)
South East Coast	2,618	18.5	141.86 (136.53-147.40)	1.16 (0.97-1.39)
South West	2,157	14.5	148.56 (142.43-154.97)	1.21 (1.01-1.45)
Wales	2,841	19.9	142.90 (137.74-148.25)	1.17 (0.98-1.40)
West Midlands	1,899	14.2	133.60 (127.73-139.75)	1.11 (0.92-1.33)
Yorkshire & Humber	459	3.3	137.50 (125.48-150.67)	1.16 (0.92-1.45)

***IRR adjusted for age, gender, calendar year, social deprivation and UK regions. CI-Confidence interval.

4.10.2 Trends in the incidence of Parkinson's disease over time

The incidence of recorded PD after adjusting for age, gender, calendar year, social deprivation and region, followed a declining trend between 2006 and 2016 using all four case definitions but less pronounced with the broadest case definition, which showed a more stable trend over time. For example, using the strictest case definition of a diagnostic Read code and at least two prescriptions of antiparkinsonian medication, the incidence of PD was 60.42 in 2006 and dropped to 42.24 cases per 100,000 PYAR in 2016 **(See Table 4-1 and Figure 4-7 and Figure 4-11)** and using the broadest case definition of a diagnosis Read code **OR** symptom Read code **OR** at least one prescription of antiparkinsonian medication, the incidence of PD was 149.20 cases in 2006 and this reduced slightly to 143.70 cases per 100,000 PYAR in 2016 **(See Table 4-2 and Figure 4-7 and Figure 4-12).**

Figure 4-11. Incidence of Parkinson's disease in THIN between 2006 and 2016 using the strictest (specific) case definition: diagnostic Read code AND at least 2 prescriptions of any antiparkinsonian medication.

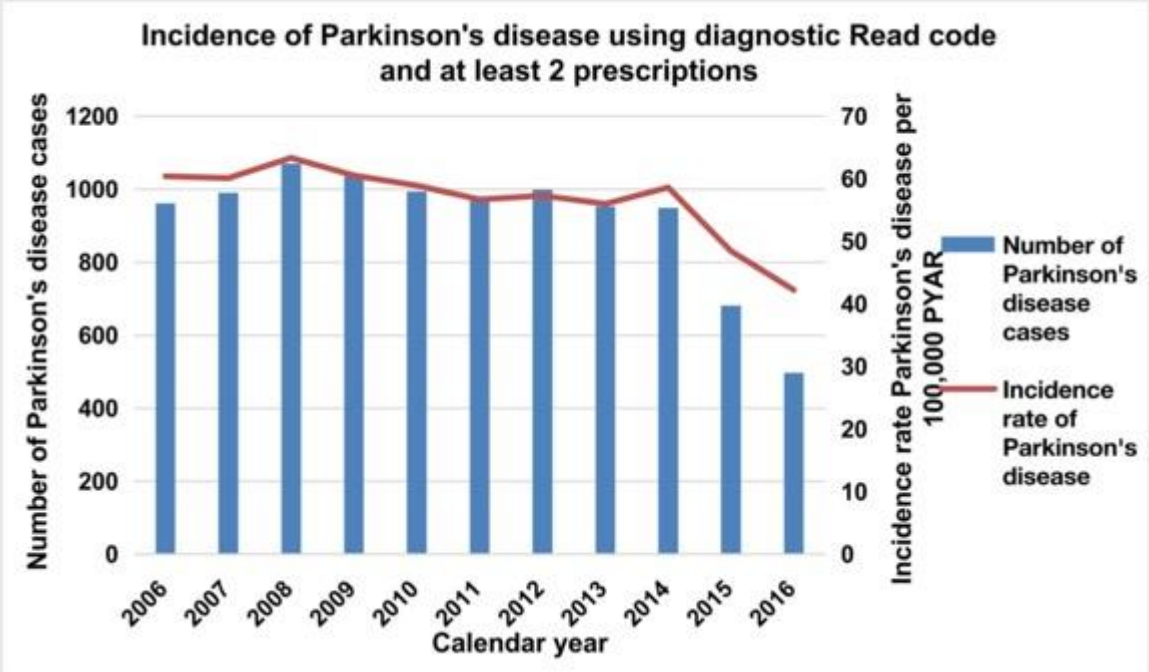
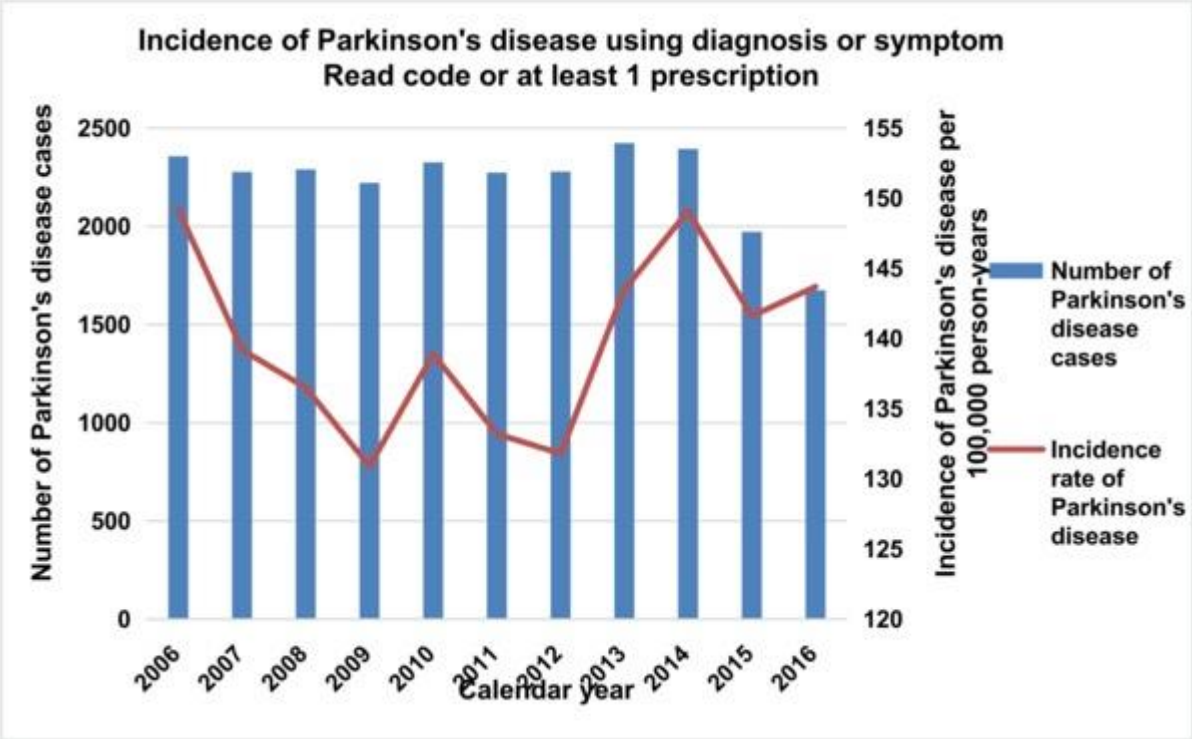


Figure 4-12. Incidence of Parkinson's disease in THIN between 2006 and 2016 using the broadest (most sensitive) case definition: diagnosis Read code OR symptom Read code OR at least 1 prescription of any antiparkinsonian medication.



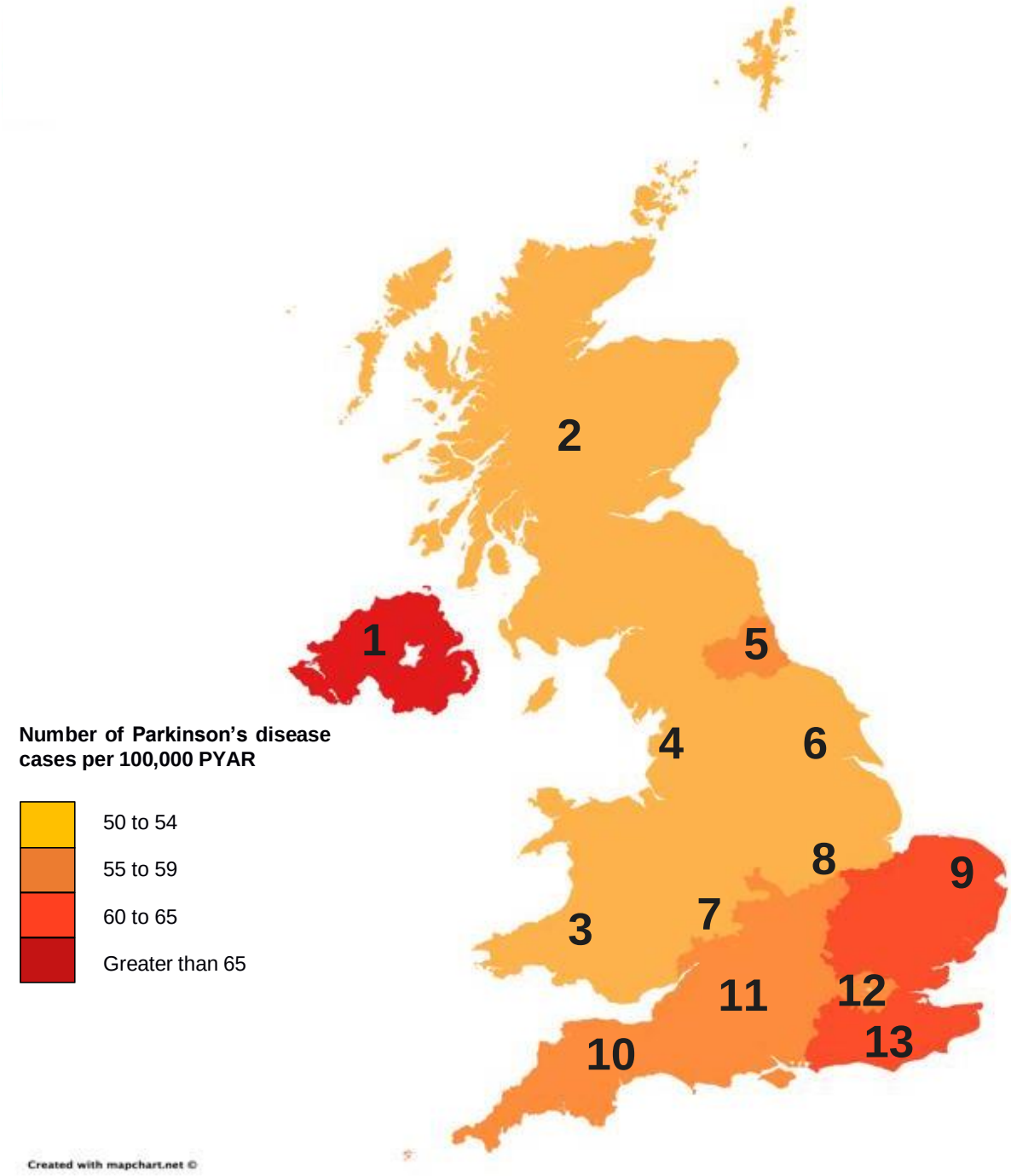
4.10.3 Relationship between incidence of Parkinson's disease and sociodemographic factors

Women had a lower incidence than men for all case definitions. Using the strictest case definition, the incidence per 100,000 PYAR was 73.18 for men and 42.66 for women (IRR: 0.52 (95% CI 0.50 to 0.55) and using the broadest case definition, the incidence per 100,000 PYAR was 151.55 for men and 128.67 for women (IRR: 0.76 (95% CI 0.74 to 0.78). Overall, the incidence of PD increased with increasing age and peaked between 80 and 89 years (for all case definitions) for example at 135.71 per 100,000 PYAR for the strictest (specific) case definition and 327.93 per 100,000 PYAR for the broadest (sensitive) case definition **(See Table 4-1 and Table 4-2 and Figure 4-15).**

General practices in Northern Ireland had the highest incidence of PD for all case definitions. For the strictest case definition, the incidence of PD for Northern Ireland was 69.00 per 100,000 PYAR in comparison to Wales (reference category) which had the lowest rate at 50.02 per 100,000 PYAR (IRR:1.46 (95%CI: 1.28 to 1.68) and for the broadest case definition, the incidence of PD for Northern Ireland was 172.18 per 100,000 PYAR in comparison to North East region (reference category) which had the lowest incidence at 116.80 per 100,000 PYAR for this case definition (IRR:1.51 (95%CI: 1.25 to 1.83). Practices in East of England had the highest incidence of PD of all the regions in England for all case definitions **(See Table 4-1 and Table 4-2 and Figure 4-13 and Figure 4-14).**

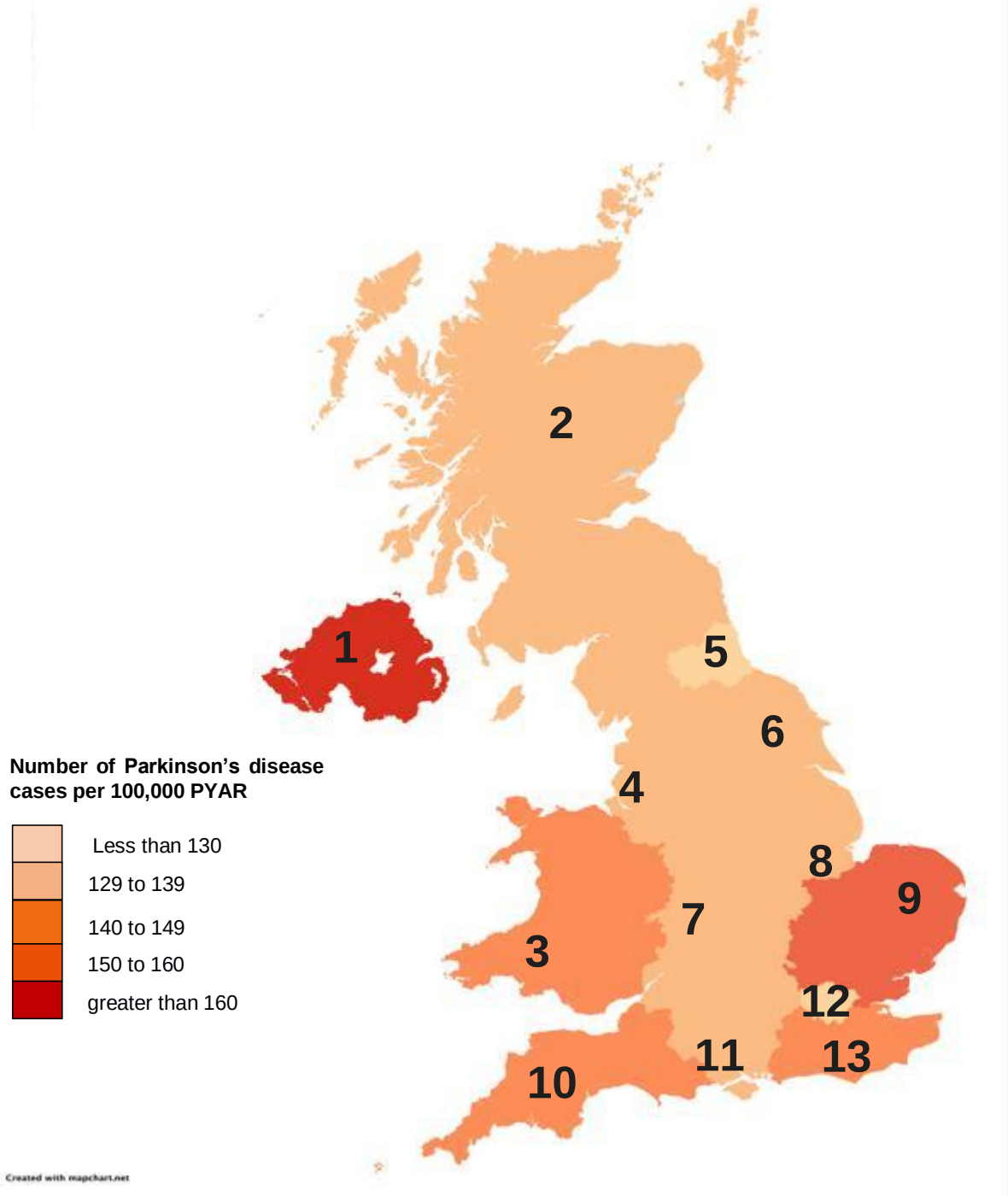
The incidence of PD was also slightly lower in people from the most deprived areas compared to those from the least deprived areas. For the strictest case definition: IRR: 0.82 (95%CI: 0.76 to 0.89), incidence per 100,000 PYAR: least deprived: 61.97; most deprived: 51.80. For the broadest case definition: IRR: 0.98 (95%CI: 0.94 to 1.02) for the most deprived quintile compared with the least deprived quintile, incidence per 100,000 PYAR: least deprived: 147.12; most deprived: 133.86 **(See Table 4-1 and Table 4-2 and Appendix 4-4 and Appendix 4-5: Table 4-3 and Table 4-4).**

Figure 4-13. Incidence of Parkinson's disease using the strictest (specific) case definition (diagnostic Read code AND at least two prescriptions of antiparkinsonian medication) per 100,000 PYAR by former Strategic Health Authority Regions from 2006 to 2016.



1. Northern Ireland 2. Scotland 3. Wales 4. North West 5. North East 6. Yorkshire 7. West Midlands 8. East Midlands 9. East of England 10. South West 11. South Central 12. London 13. South East Coast. Image created with mapchart.net.

Figure 4-14. Incidence of Parkinson's disease using the broadest case definition (diagnosis Read code OR symptom Read code OR at least 1 prescription of antiparkinsonian medication) per 100,000 PYAR by former Strategic Health Authority Regions from 2006 to 2016.



1. Northern Ireland 2. Scotland 3. Wales 4. North West 5. North East 6. Yorkshire 7. West Midlands 8. East Midlands 9. East of England 10. South West 11. South Central 12. London 13. South East Coast. Image created with mapchart.net.

4.10.4 Incidence of Parkinson's disease by age group

The incidence rate of recorded PD between 2006 and 2016 increased with increasing age up to the age group 80 to 89 years using all four case definitions and declined in the oldest age group **(See Figure 4-15).** The slightly declining trend in incidence rate over time was similar across all age groups using the stricter case definitions **(See Figure 4-16 and Appendix 4-6 and Appendix 4-7)** and rates were stable using the broadest case definition (**See Figure 4-17).**

Figure 4-15. Incidence of Parkinson's disease in THIN increasing with increasing age between 2006 to 2016 using all case definitions.

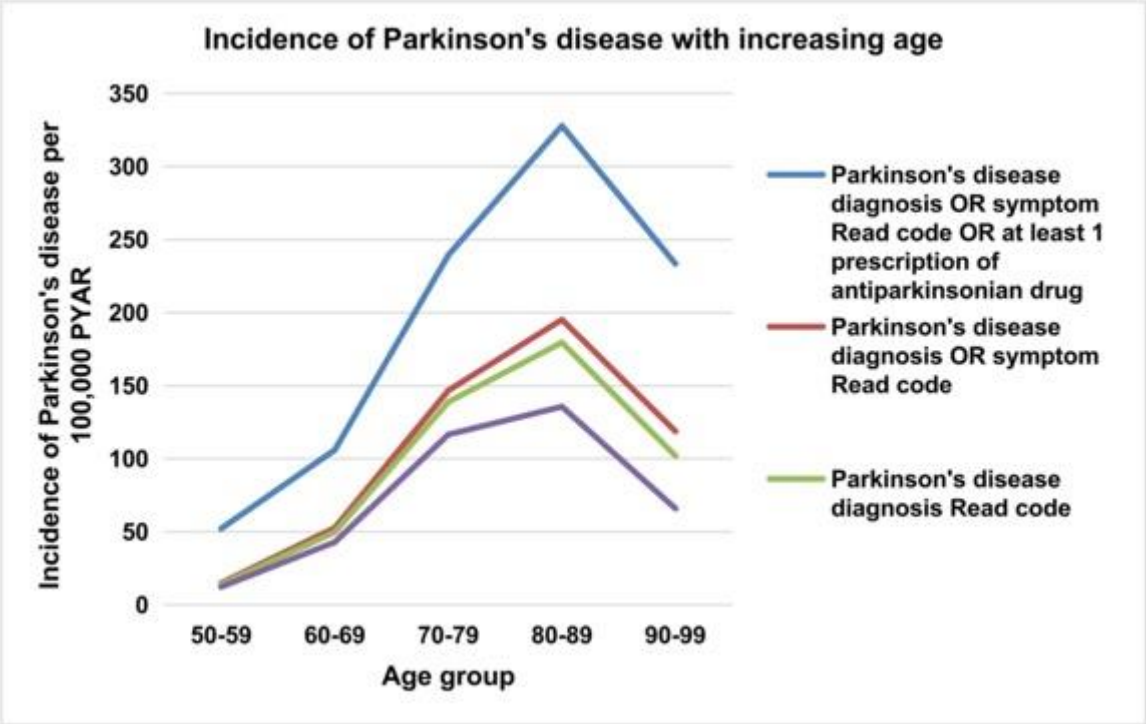


Figure 4-16. Incidence of Parkinson's disease in THIN by age group between 2006 to 2016 using the strictest (specific) case definition (diagnostic Read code AND at least 2 prescriptions of antiparkinsonian medication).

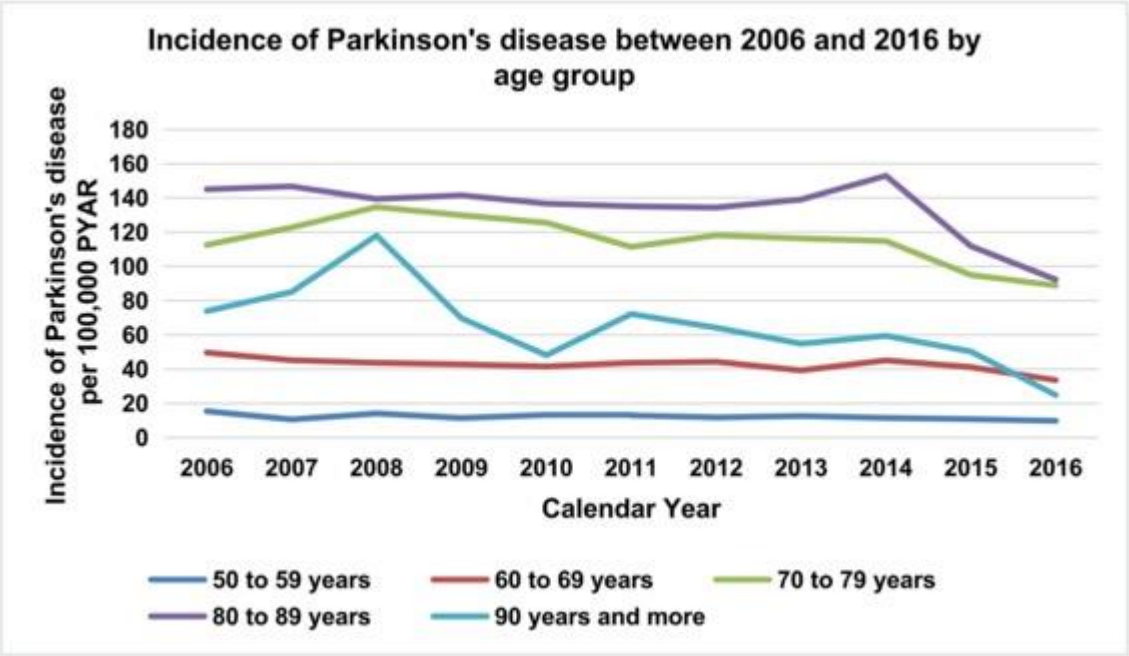
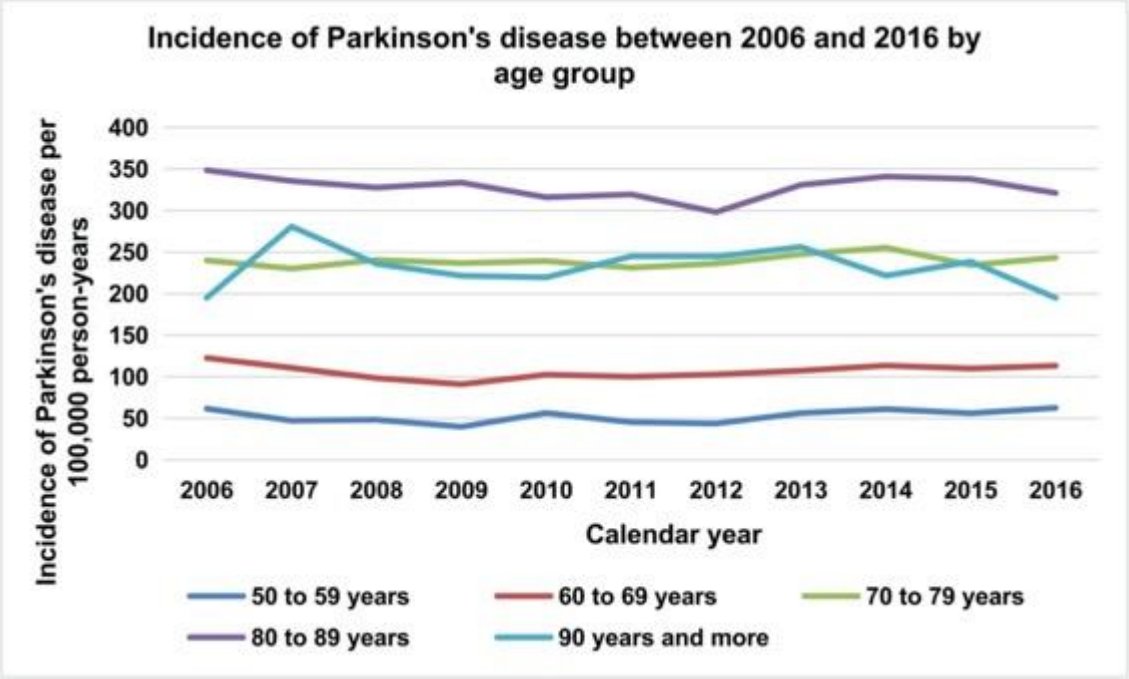


Figure 4-17. Incidence of Parkinson's disease in THIN by age group between 2006 to 2016 using the broadest (most sensitive) case definition (diagnosis Read code OR symptom Read code OR at least 1 prescription of antiparkinsonian medication).



4.10.5 Incidence of Parkinson's disease by gender

The incidence of recorded PD was higher in males compared to females over the time period and slowly declined for both sexes, particularly for the strictest case definition. Using the strictest case definition: Male; 2006: 73.18 per 100,000 PYAR, 2016: 59.67 per 100,000 PYAR. Female; 2006 49.04 per 100,000 PYAR, 2016: 26.32 per 100,000 PYAR) **(See Figure 4-18).** For the other case definitions, incidence in men remained stable while it slowly declined over the time period in women. For the broadest case definition: (Male; 2006:162.33 per 100,000 PYAR, 2016: 161.83 per 100,000 PYAR. Female; 2006 137.61 per 100,000 PYAR, 2016: 127.06 per 100,000 PYAR) **(See Figure 4-19 and Appendix 4-8 and Appendix 4-9)**

Figure 4-18. Incidence of Parkinson's disease in THIN by gender between 2006 to 2016 using the strictest case definition (diagnostic Read code AND at least 2 prescriptions of antiparkinsonian medication).

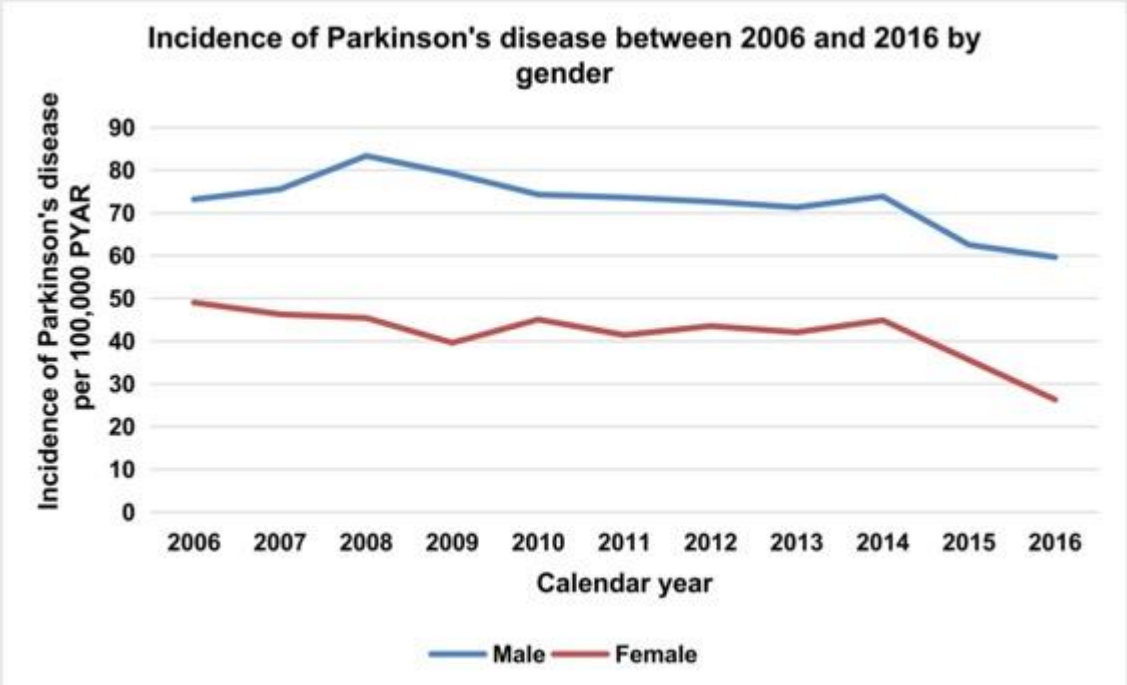
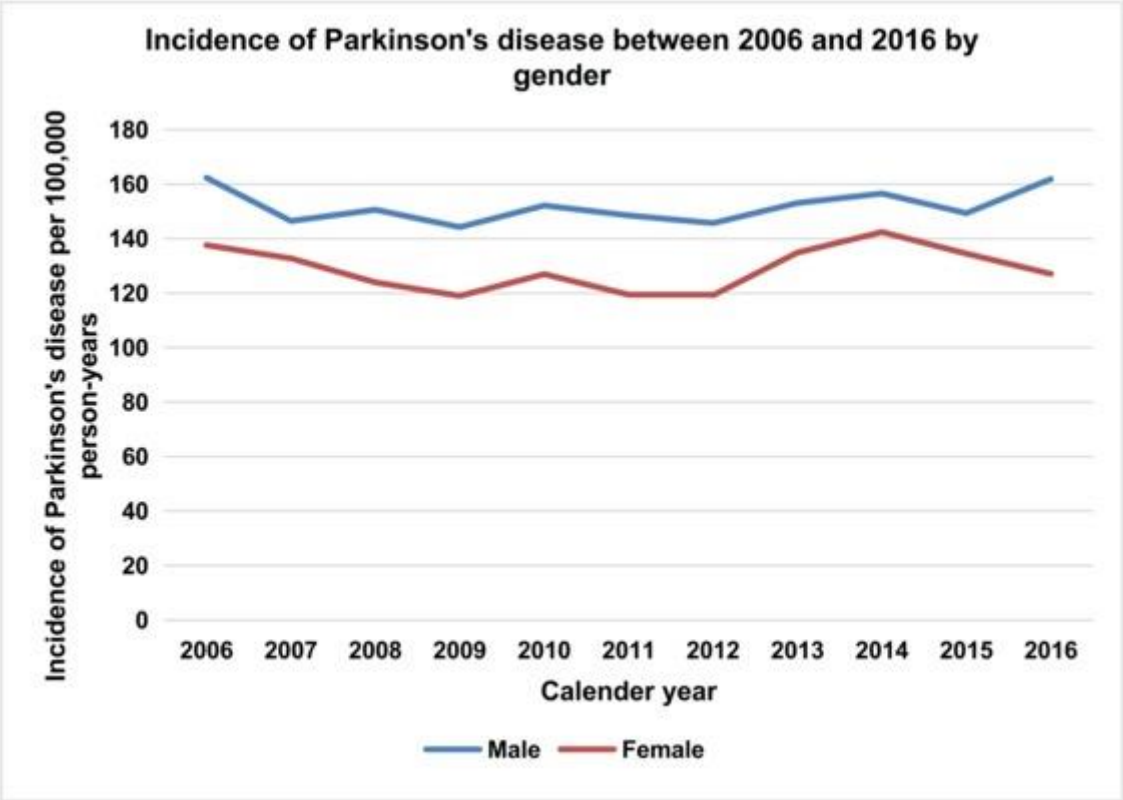


Figure 4-19. Incidence of Parkinson's disease in THIN by gender between 2006 to 2016 using the broadest case definition (diagnosis Read code OR symptom Read code OR least 1 prescription of antiparkinsonian medication).



4.10.6 Incidence of Parkinson's disease by degree of social deprivation

The incidence of recorded PD throughout the study period was higher in individuals who were from the least deprived (most affluent) compared to those who were most deprived. For the strictest case definition: least deprived – Townsend 1 and 2; 2006: 62.0 per 100,000 PYAR, 2016: 43.93 per 100,000 PYAR, most deprived – Townsend 4 and 5; 2006 61.69 per 100,000 PYAR, 2016: 38.52 per 100,000 PYAR (**See Figure 4-20)**. For the broadest case definition: least deprived – Townsend 1 and 2; 2006: 160.95 per 100,000 PYAR, 2016: 148.17 per 100,000 PYAR, most deprived – Townsend 4 and 5; 2006: 143.88 per 100,000 PYAR, 2016: 142.81 per 100,000 PYAR) **(See Figure 4-21 and Appendix 4-10 and Appendix 4-11).**

Figure 4-20. Incidence of Parkinson's disease in THIN by degree of social deprivation between 2006 to 2016 using the strictest (specific) case definition (diagnostic Read code AND at least 2 prescriptions of antiparkinsonian medication).

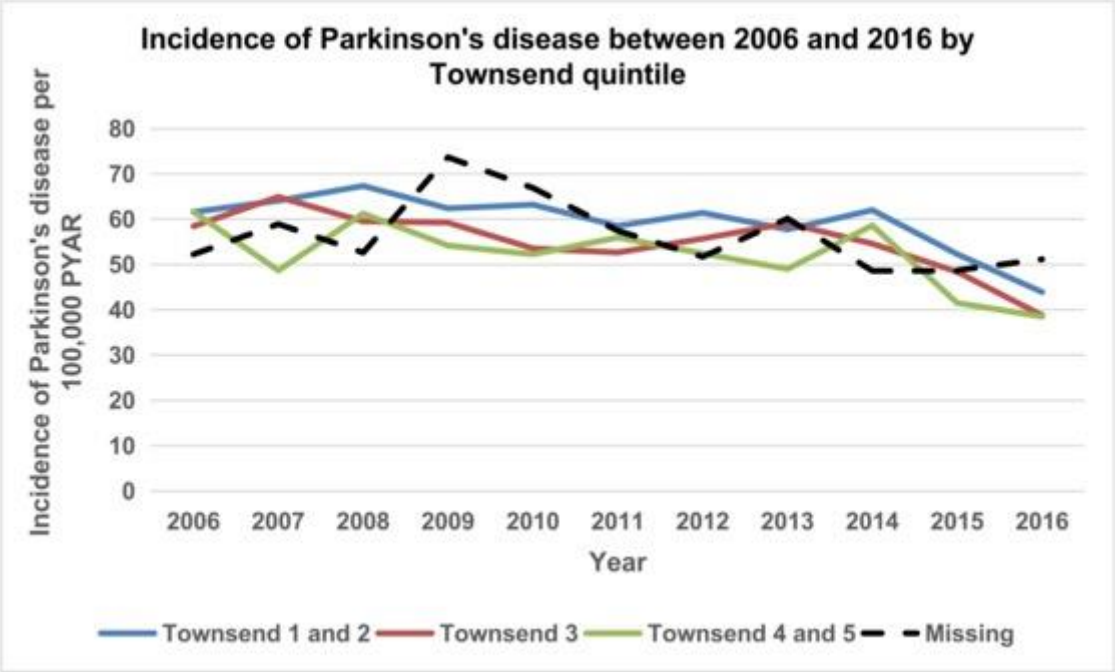
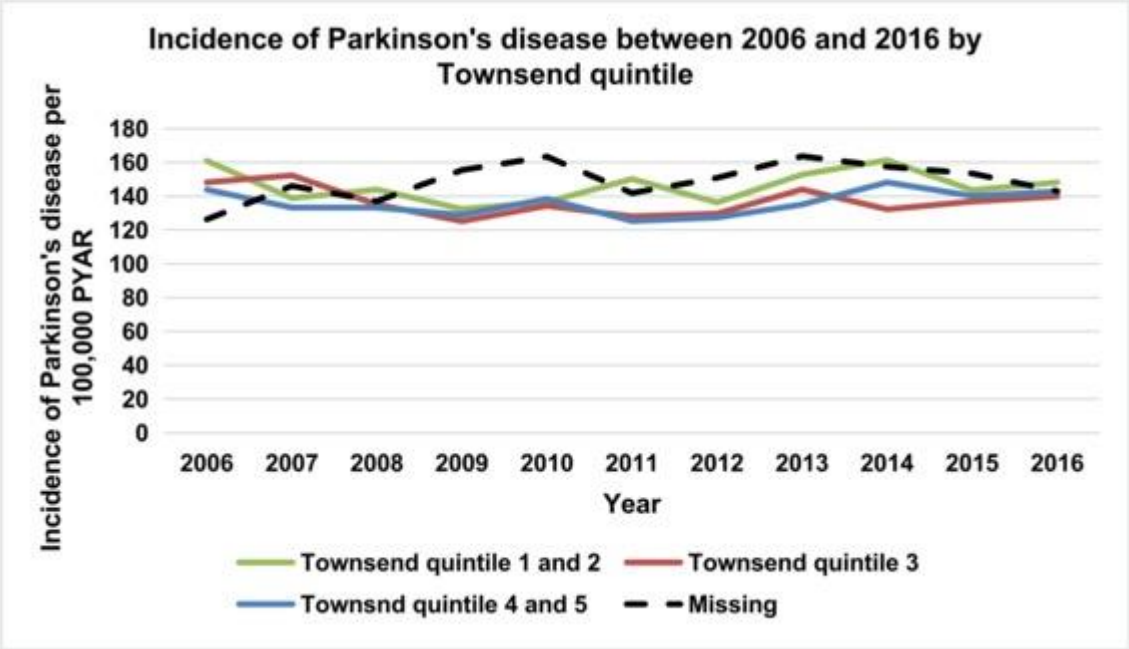


Figure 4-21. Incidence of Parkinson's disease in THIN by degree of social deprivation between 2006 to 2016 using the broadest case definition (diagnosis Read code OR symptom Read code at least 1 prescription of antiparkinsonian medication).



4.10.7 Incidence of Parkinson's disease by geographical region

The incidence of recorded PD was highest in Northern Ireland all through the time period of the study compared to England, Scotland and Wales. The incidence of PD slowly decreased across all the regions for the stricter case definitions. Using the strictest case definition: Northern Ireland; 2006: 61.83 per 100,000 PYAR, 2016: 49.77 per 100,000 PYAR **(Figure 4-22).**

The incidence of PD increased in Northern Ireland during the study period rising in 2012 for the broadest case definition: Northern Ireland; 2006: 181.26 per 100,000 PYAR, 2016: 201.68 per 100,000 PYAR **(Figure 4-23 and Appendix 4-12 and Appendix 4-13).**

Figure 4-22. Incidence of Parkinson's disease in THIN by geographical region between 2006 to 2016 using the strictest (specific) case definition (diagnostic Read code AND at least 2 prescriptions of antiparkinsonian medication).

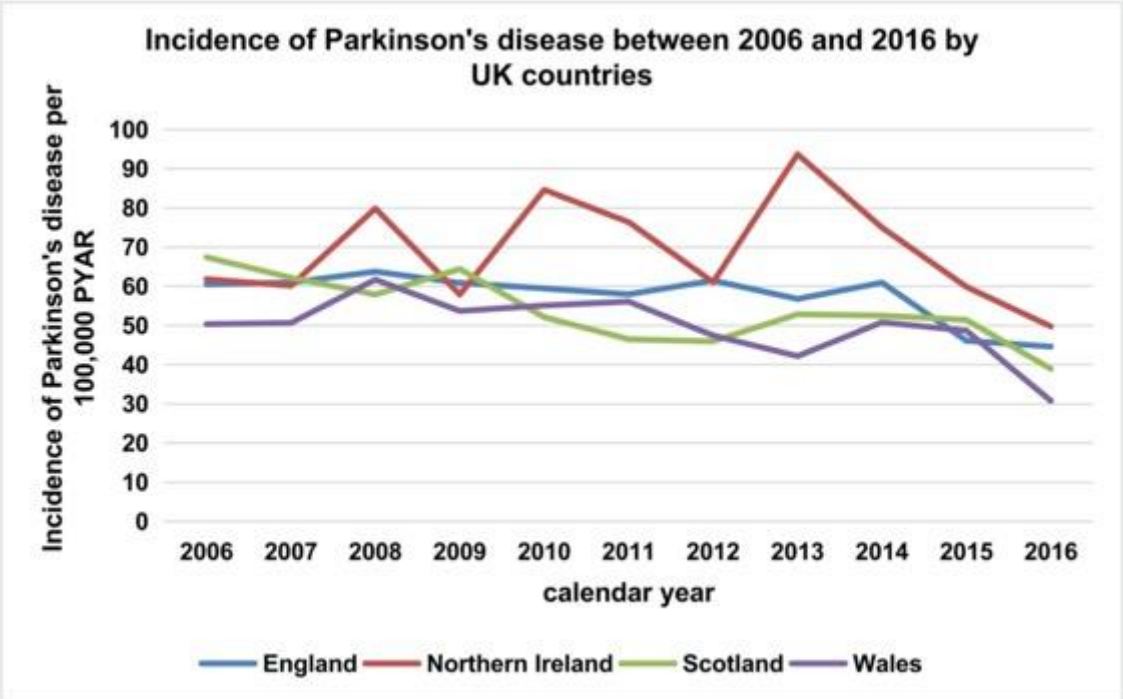
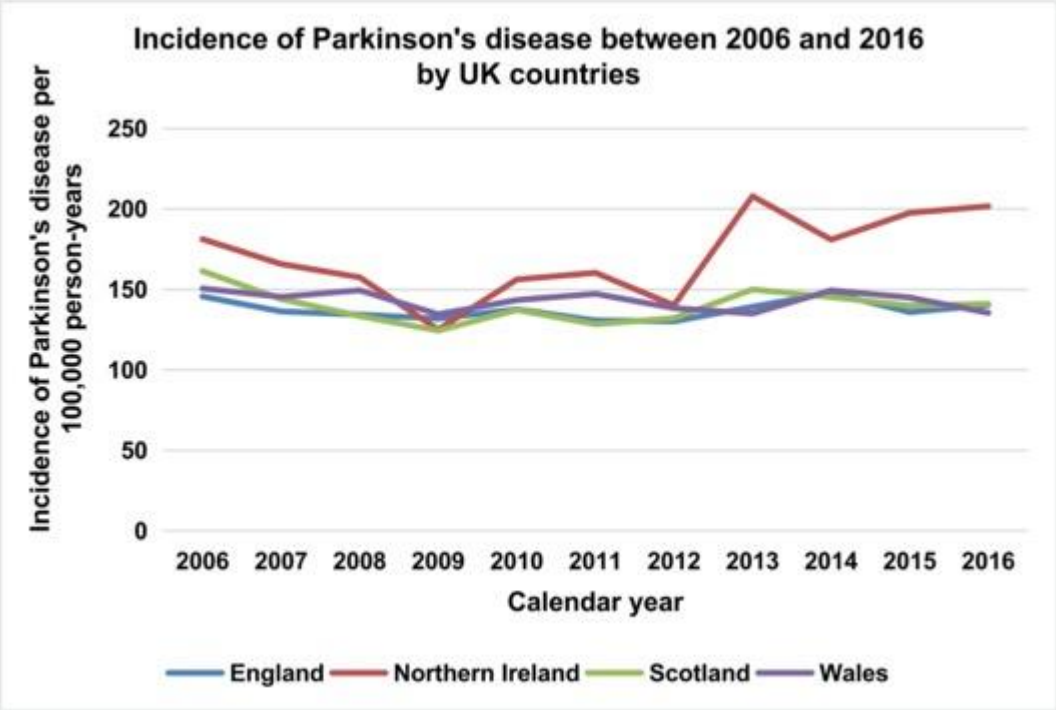


Figure 4-23. Incidence of Parkinson's disease in THIN by geographical region between 2006 to 2016 using the broadest (sensitive) case definition (diagnosis Read code OR symptom Read code OR at least 1 prescription of antiparkinsonian medication).



4.11 Discussion

4.11.1 Summary of main findings

This study revealed that the incidence of PD recording in THIN, a large UK primary care database was stable using the most sensitive (broadest) case definition (PD diagnosis **OR** symptom Read code **OR** at least 1 prescription of antiparkinsonian medication) and the incidence of PD decreased between 2006 and 2016 using the stricter case definitions: [1] diagnosis Read code **AND** at least 2 prescriptions (validated case definition), [2] PD diagnosis Read code, [3] PD diagnosis **OR** symptom Read code. Those in the older age group were more likely to receive a diagnosis of PD compared to those in the younger age group, except the oldest age group (90 years and more) where the incidence rate was lower. Men were more likely to be recorded with a diagnosis of PD compared to women. The incidence of PD was highest in Northern Ireland and those who live in a least deprived area were more likely to receive a diagnosis of PD compared to those who lived in the most deprived areas.

4.11.2 Interpretation of the results within the context of available literature

I found that the incidence of PD in a large UK primary care database as seen in this study was stable using the broadest case definition between 2006 and 2016. The incidence of PD using the three stricter case definitions decreased slightly, particularly using the strictest definition requiring a PD diagnosis Read code and at least 2 prescriptions of antiparkinsonian medication. It is likely that the decrease in incidence with the stricter case definitions reflects changes in diagnostic practice or coding by general practices (Horsfall L et al., 2013). The

higher rate in incidence using prescription data may be more accurate as there is no incentive for PD coding in primary care and combining prescriptions of antiparkinsonian medications in addition to diagnosis codes may better reflect true actual incidence rates. THIN is recognized to be a suitable database for work in drug utilization due to its accuracy in prescription coding (Blak BT et al., 2011).

Worldwide, the age-adjusted incidence of PD has been estimated to have increased by 6.6% between 1990 and 2019 in the Global Burden of Disease study (Deuschl G et al., 2020, GBD 2019 Diseases and Collaborators, 2020). Much of this change may reflect changes in the still high rates of underdiagnosis, particularly in health care systems with low availability of neurological services. Few studies directly exploring changes in incidence rates in the same population have been published, and these have provided inconsistent results. A longitudinal study in the US found an increase in age-adjusted incidence rates of PD for men, particularly over the age of 70 years, from 1976 to 2005 (Savica R et al., 2016). For a more recent time period, a study in Taiwan reported an increase in PD incidence from 2002 to 2009 from 33.5 to 36.6 per 100,000 based on a national health service insurance database (Liu C et al., 2016), and a study from Finland reported a slight increase in age-adjusted incidence of PD between 1997 to 2014 (Isotalo J et al., 2017). Additionally, a study from South Korea reported an increase in the period from 2010 to 2015 from 73.2 per 100,000 to 88.7 per 100,000 among people aged 50 years and more (Park JH et al., 2019). On the other hand, a previous US study in Olmsted county did not report a change in incidence of PD between 1976 and 1990 (Rocca W et al., 2001), and in a US study using

Medicare data the incidence of PD remained stable between 1992 and 2005 (Akushevich I et al., 2013). In a Canadian study the incidence of PD also remained relatively constant between 1990 and 2007 (Lix LM et al., 2010). A study from Taiwan reported a decrease in overall incidence from 35.3 per 100,000 to 28.8 per 100,000 from 2005 to 2011 (Liu WM et al., 2016). Similarly, the Rotterdam study from the Netherlands reported a stark decline in PD incidence from 1990 to 2010 (Darweesh SK et al., 2016). In the UK, my results from 2006 to 2016 are slightly lower than those in a previous study conducted in the same database over an earlier time period, which had similarly found a stable incidence rate using a broad definition (Horsfall L et al., 2013). Another study in the UK (Parkinson's UK: Reference Report, 2017), using a different but comparable dataset, also reported no change in incidence rates between 2011 and 2015.

It is unclear why there are differences in trends in incidence between these studies in different geographical regions and time periods. It is possible that there are environmental or genetic factors that differ between geographical areas and over time. For example, smoking which is known to be negatively associated with PD has become less prevalent in many countries, but so have, conversely, exposure to pesticide and other environmental risk factors that have been associated with an increased risk of PD (Poewe W et al., 2017). However, it is also possible that despite best efforts, methodological differences, such as residual changes in diagnostic coding or case ascertainment may account for discrepancies in these studies (Wickremaratchi MM et al., 2009), and greater awareness and higher diagnostic rates are likely to be particularly relevant where a decrease in incidence in the older age

groups are seen (Park JH et al., 2019) as difficulties with movement may be misinterpreted as due to other comorbidities.

Overall, the incidence rates of PD in this study are comparable to other studies in European populations (van de Vijver DA et al., 2001, von Campenhausen S et al., 2005). In addition, the study by Parkinson's UK using a different but comparable dataset (Parkinson's UK: Reference Report, 2017), reported an incidence rate of 71 per 100,000 in individuals aged 50 to 94 years between 2011 and 2015 using the diagnostic code for PD, which is similar to our incidence rate of 70 per 100,000 using this diagnostic code in this age group.

In keeping with other studies, I also found an increase in incidence rate with age (MacDonald BK, 2000, Tanner C et al., 2003, Alves G et al., 2009, Linder J et al., 2010, Winter Y et al., 2010, Horsfall L et al., 2013, Duncan GW et al., 2014), except in the oldest age group (90 years and more) where incidence rate was lower which may reflect underdiagnosis of PD in the oldest age group (Duncan GW et al., 2014, Hirsch L et al., 2016). Men were more likely to be recorded with a diagnosis of PD compared to women in keeping with previous research (Foltynie T et al., 2004, Alves G et al., 2009, Linder J et al., 2010, Duncan GW et al., 2014). The incidence of PD was highest in those who live in more affluent areas compared to those who lived in the most deprived areas. This difference was similar for all case definitions and also reported in the previous study (Horsfall L et al., 2013). This could reflect lower rates of health seeking behaviour or diagnosis in lower socioeconomic groups, and could be due to confounding factors such as smoking which is linked to lower risk of PD

(Allam MF et al., 2004, Breckenridge CB et al., 2016), and also well established to be associated with deprivation (Hiscock R et al., 2012, ONS, 2018).

After controlling for age, gender, calendar year, region and social deprivation, the incidence rate of PD was highest in Northern Ireland. There are no previous studies to compare but a recent report on prevalence and incidence of PD by Parkinson's UK showed PD incidence was highest in England using another routine data source (the Clinical Practice Research Datalink (CPRD)) (Parkinson's UK: Reference Report, 2017). Also, there could be other confounders such as smoking which is known to be associated with reduced risk of developing PD. It is reported that since 2011, the proportion of current smokers in England, Scotland, Wales and Northern Ireland has declined significantly but the estimate over time for Northern Ireland has remained variable because of smaller sample size (ONS, 2019).

4.12 Strengths and limitations of this study

The strength of this study is that the data were derived from routinely collected electronic health records of a large population of patients from many general practices over an eleven-year time period. This allowed me follow up a large cohort of patients which are largely representative of UK general population without any major change in ascertainment method (Blak BT et al., 2011). The large number of individuals included in the analysis enabled me to calculate estimates by age group, gender, socioeconomic status, calendar year and region. In addition, the use of routinely collected prospective data captures cases without recall or selection bias in diagnosing PD in primary care. In addition, I used a definition for PD to allow for changes in diagnostic and

coding patterns, as well as more stringent diagnostic definitions. All these did not suggest an increase in incidence of PD in the UK.

Another strength of this study is that data on age, gender, prescriptions, region were complete, and the only missing data was on social deprivation. However, the incidence rates of PD were higher in those with missing data and so likely not missing at random. There is a possibility that those with missing data on social deprivation are in more affluent areas as there was no linked postcode available and this is often the case where a new housing estate has been built, which often have a younger more affluent population.

The main limitation of this study is that I could not confirm the diagnosis of PD, I depended on clinician recording of the diagnosis of PD in electronic heath records instead of systematic evaluation of cases. Although I used four different case definitions which involved not only diagnosis codes but treatment and symptom variables, there may still be some misclassification if a diagnosis of PD was not considered. The broadest case definition is likely to be more sensitive but with corresponding reduced specificity and there are likely to be some false positives (and for the strictest case definition more false negatives). However, a previous validation study has shown that the strictest case definition has good specificity of PD (Alonso A et al., 2007). In addition, I adjusted only for age, gender, calendar year, social deprivation and region. Some of the observed differences in incidence rates may be explained by other confounding factors which I have not accounted for, for example ethnicity and smoking due to large amount of missing data for these variables. Finally, the use of GP records for investigating incidence of PD meant that the results of

the analysis are confined to those registered with a general practitioner and rates may be different in the small number of people not registered with a GP (commonly those who are homeless or asylum seekers etc), but the numbers of the population not registered with primary care in the UK is very small (2%) (Stagg HR et al., 2012, Elwell-Sutton T et al., 2017, ONS, 2018, ONS, 2019).

4.13 Context of this chapter on overall research

In this chapter, I have described four case definitions used to estimate the incidence of PD in THIN. I have examined the trends in incidence of PD recordings over eleven years (2006 to 2016) and showed that there has been a slight decline in recordings over this time period using all but the broadest (most sensitive) case definition which showed a more stable trend. Although the rate of decline reported differs from previous report based on case definition, there are similar associations with age, gender and social deprivation. The importance of the findings from this chapter on clinical, and public health practice and future research directions will be discussed in my final discussion (Chapter 7).

In the next chapter, I describe the process of exploring mortality in those with a recording of PD in comparison to those without PD in primary care using data from THIN.

Chapter 5 Mortality of people with Parkinson's disease in a large UK-based cohort study. Time trends and relationship with disease duration.

5.1 Chapter overview

Having reported that people with PD are hospitalised particularly in advanced disease and investigated reasons for hospitalisation which could also lead to death (Chapter 2), I then examined mortality in PD compared with frequency-matched controls without PD focusing on time trends and disease duration in this Chapter. Thereafter, I investigated factors associated with mortality in people with PD compared to frequency-matched controls, presenting methods, results, discussion, strengths and limitations of the study. findings from this chapter will help gain insight into how mortality of people with PD (using incident cases from Chapter 4) compares to that in individuals without PD. The paper based on this chapter was published online on the 5th of August in Movement Disorders Journal and included in **Appendix 5-1.**

5.2 Study background

Despite recent developments in the treatment of PD, mortality in PD is increased in comparison to the general population (Hughes TA et al., 2004, Macleod AD et al., 2014, Hobson P and Meara J, 2017). However, previous population-based studies used prevalent cohorts with varying duration of disease rather than use more informative incident cohorts which have been followed up from diagnosis, leading to possible overestimation of mortality (Berger K et al., 2000, Fall PA et al., 2003, Hobson P and Meara J, 2004, de Lau LML et al., 2005, D'Amelio M et al., 2006, Buter TC et al., 2008, Posada IJ

et al., 2011). Other population-based mortality studies have included patients with progressive supranuclear palsy, multiple system atrophy and cortico-basal degeneration with higher mortality (Herlofson K et al., 2004). Others recruited patients from movement disorder clinics which may not be fully representative and carry risk of selection bias (Auyeung M et al., 2012).

Over the last decade (ONS, 2016, PHE, 2018), age-adjusted mortality over the age of 50 years has been on the decline in the UK but there are no data whether this is the same for people with PD. Although the availability and use of symptomatic treatments for PD, including pharmacological, non-pharmacological and surgical treatments has changed considerably over time, there are still no disease-modifying treatments to date (Kalia LV and Lang AE, 2015, Poewe W et al., 2017). Current available treatments are intended to improve the quality of life of patients with PD, but whether they have any effect on life expectancy remains unclear. Thus, further work is needed to explore recent time trends in mortality in an incident PD population.

5.3 Study aim

- To explore mortality in people with PD in UK primary care in comparison to people without PD between 2006 and 2016.

5.4 Study objectives

- To estimate overall mortality in people with PD compared to people without PD.
- To explore the association of mortality in people with PD with disease duration.

- To investigate how mortality rates have changed in relation to age, gender, and social deprivation.

5.5 Methods

5.5.1 Data source

The THIN dataset was used for this study **(See Chapter 3,** sections **3.2.5, 3.4 to 3.7)**.

5.5.2 Study population

All individuals aged 50 years and more and had been actively registered with a general practice for at least six months during the study period 1st of January 2006 to 31st of December 2016 were included in the analysis (n=3,195,391). The index date was the earliest date of PD diagnosis Read code recording or antiparkinsonian drug code recording. Participants entered the cohort if they met the inclusion criteria or on the randomly matched date (index date) for the control group (non-PD cohort). They were followed up until they died, de-registered with the general practice or the practice stopped contributing data to THIN, whichever was earliest.

5.5.3 Exclusion criteria

My exclusion criteria were:

- All individuals with a history of PD prior to study entry.
- All individuals with restless leg syndrome who have been treated with dopamine agonists.

- Individuals with a diagnosis of PD in the first six months after registration with a practice. This could represent a recording of a retrospective medical information rather than a true new recording of PD (Lewis JD et al., 2005).
- All other individuals with less than six months of data from registration within a general practice.
- For analysis on mortality time trends and disease duration, I started the study period one year from the index only for those entering before and during 2007 to avoid follow-up time being too short for deaths to occur.

5.5.4 Study participants

5.5.4.1 PD cohort

This consisted of all individuals aged 50 years and more with first ever PD diagnosis Read code and at least two prescriptions of any of the five major classes of antiparkinsonian medication during the time period of 1st of January 2006 to 31st of December 2016 **(section 4.4.4 in Chapter 4 and Section 5.5.4.2).**

5.5.4.2 Identification of incident cases.

In order to identify incident cases of PD used for the cohort studies in this thesis, the strictest (most specific) case definition was used. Each case of PD was identified using a first recording of diagnosis Read code and at least two prescriptions of any of the five main groups of antiparkinsonian medications (Levodopa-containing medications, Dopamine-agonists, MAO-B inhibitors,

COMT inhibitors and Amantadine). This case definition was previously validated (90% validity) in another similar database-General Practice Research Database (GPRD) (Alonso A et al., 2007) in which there is an overlap with THIN in about 60% of patients (Lu N et al., 2016) and used in a previous study (Schrag A et al., 2015).

Through searching THIN, 10,104 individuals with a first recording of PD diagnosis and at least two prescriptions were identified between 2006 and 2016. In order to identify electronic recording of PD, I created Read code lists for PD diagnosis and drug code lists using previously published guidelines (Dave S and Petersen I, 2009) **(see Appendix 4-1)**. A summary of the identification process at each stage of the algorithm is shown in **Figure 5-1.**

5.5.4.3 Generating code lists

Code lists were developed to extract relevant records for this study. These include code lists for PD, PD related symptoms and drug codes for antiparkinsonian medications. These code lists were developed using a framework based on methods which have been previously described. For example, in creating a code list for PD, a list of key words and synonyms related to PD were identified through discussions with two of my supervisors who are clinicians and familiar with the database (AS and KW). The entire Read code list was searched in THIN for the following: “Parkinson’s disease”, “Parkinson's disease NOS”, “Parkinsonism with orthostatic hypotension” and “Dementia in Parkinson's disease” using a Stata loop. The identified list of codes was reviewed while excluding irrelevant codes resulting in a final code list for PD. This code list was then reviewed and approved by the entire team

before being used for extraction of data. Read codes lists used for data extraction in this thesis were generated as described above and can be found in the Appendix:

- Code lists developed for PD incidence study (code lists used for extraction of PD, PD symptoms and drug codes for antiparkinsonian medications) – **See Chapter 4: Appendix 4-1.**
- Code lists developed for PD mortality study (code lists used for extraction of PD, PD symptoms and drug codes for antiparkinsonian medications) – **See Chapter 4: Appendix 4-1.**
- Code lists developed for PD hospitalisation study (code lists for admissions/discharge, reasons for admissions: falls, fractures, infections, stroke, electrolyte imbalance, surgical procedures, heart failure, myocardial infarction/ischaemic heart disease) – **See Chapter 6: Appendix 6-1.**

Figure 5-1. Process of identification by computer search in THIN, of people with Parkinson's disease using diagnosis Read code and at least two prescriptions of antiparkinsonian medication.

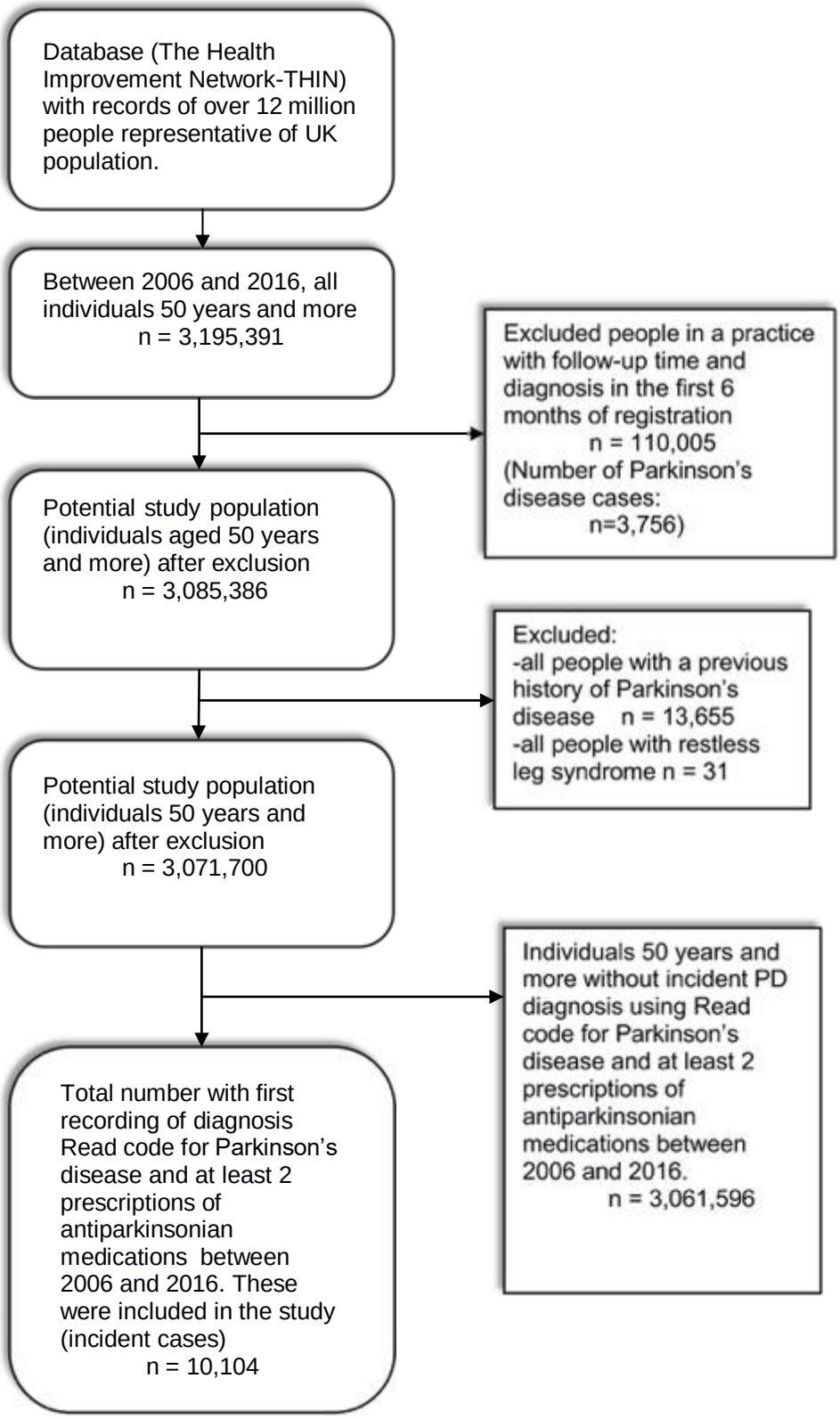


Figure 5-1 was taken from published manuscript by Okunoye et al in MDS journal and provided in full for reference in Appendix 5-1.

5.5.4.4 Non-PD cohort (general population)

This comprised of a random sample of up to six people with no record of PD who were frequency-matched within each practice by age, gender and calendar year using a randomly assigned index date **(see Figure 5-2).**

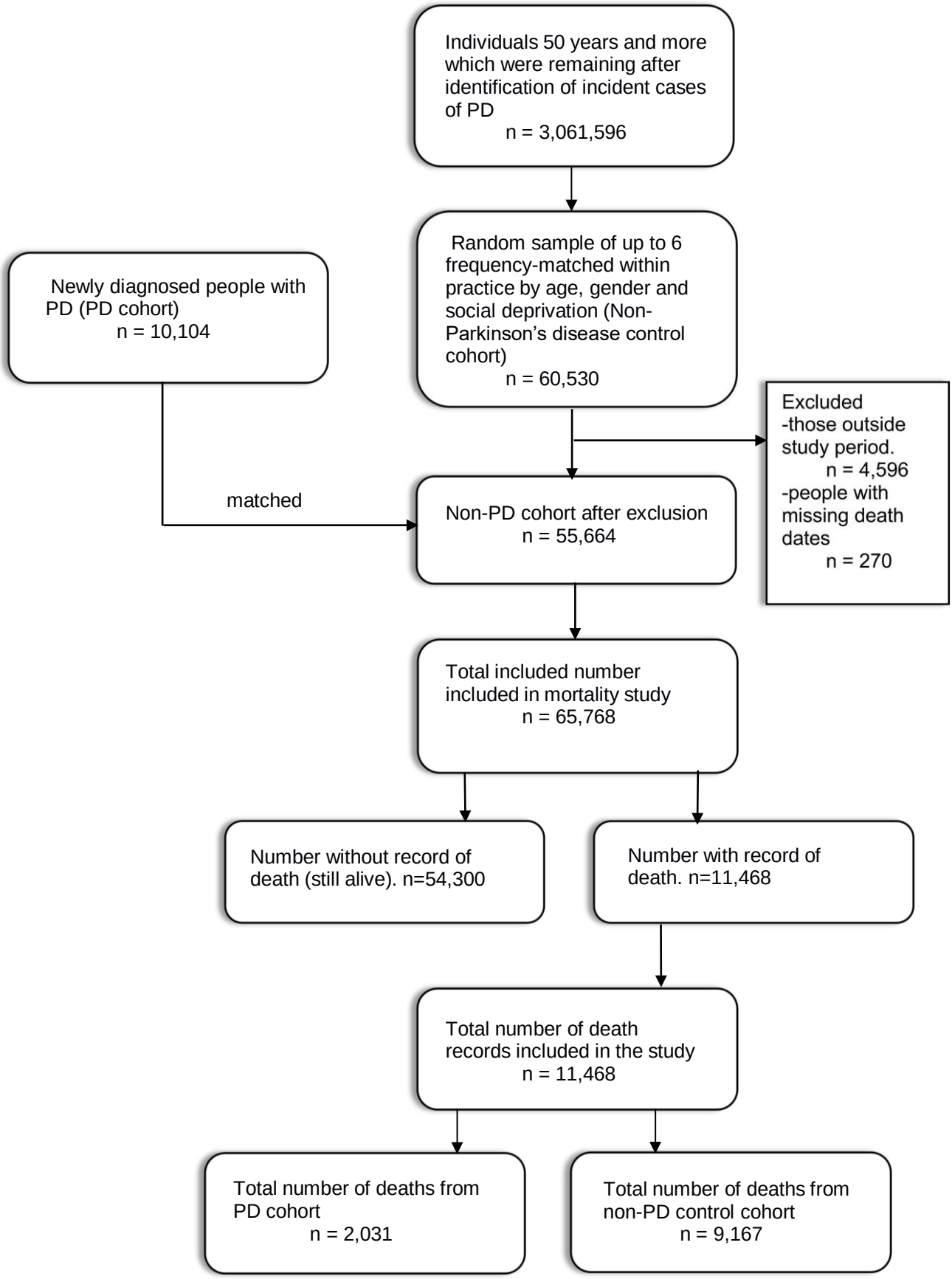
5.5.4.5 Outcome

Mortality was the main outcome. I identified Individuals who died during the follow-up through their death records in THIN **(see Figure 5-2)**.

5.5.4.6 Mortality Reporting in THIN

The AMR (Acceptable Mortality reporting) is quality filter for THIN. The AMR date is the year from which each general practice is expected to have records of mortality which are equivalent to that from national statistics (QuintilesIMS, 2017). This is derived by reviewing reports of trends in death recording for individual practice contributing data to THIN against reports of predicted numbers of deaths generated from the Office for National Statistics (ONS) accounting for the demographics of the practice (QuintilesIMS, 2017, Maguire A et al., 2009). I used all practices which are considered to be reporting all-cause mortality comparable to these statistics. Records of death are assigned a death date which I used to identify individuals who died during follow-up (**see Chapter 3).**

Figure 5-2. Process of identifying mortality study cohort and those who died.



5.6 Statistical Analysis

For descriptive purposes, mortality was categorised by calendar year, social deprivation (Townsend quintile) and ten-year age-groups: 50 to 59 years, 60 to 69 years, 70 to 79 years, 80 to 89 years and 90 years and more.

In order to estimate adjusted mortality rates, a multivariable Poisson model was used. Age was used as the timescale while data on age and calendar year were split by one-year intervals. Unadjusted and mutually adjusted mortality rates and rate ratios for age, gender, calendar year, time since diagnosis or index date, smoking and social deprivation by PD status (people with and without PD) were estimated. I tested for multiplicative interactions between PD status and each of these variables. Multivariable Poisson regression analyses was used to calculate the mortality rate ratios and the marginal effects (adjusted mortality rates) adjusted for age group and other covariates.

Whilst rate ratio scale has a baseline comparator, marginal effect on the other hand, is a measurement of how much the mortality rate is predicted to vary per unit change in an exposure variable. Marginal effects for fixed values of calendar year were estimated while holding all other parameters at their observed values in the model and applying the delta method for estimation of the standard errors. Non-linear associations of mortality with age and calendar year were explored using restricted cubic spline interpolation. Linear models with different spline transformations (3-5 knots) were compared. The Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to check whether additional knots or cubic spline transformations improved the model fit while avoiding unnecessary complexity. Wald tests

were used to estimate the p-values for categorical variables and multiplicative interaction terms. In order to account for the effects of clustering of observations within general practices, practice identifiers were included, and robust standard errors were calculated. In order to investigate overdispersion in the analyses, negative binomial models were run, and outputs were compared.

5.7 Ethics and data permissions

See Chapter 3 (Section 3.4) and **Appendix 3-1.**

5.8 Results

5.8.1 Demographic features

Seven hundred and four general practices met the criteria for acceptable mortality and data recording within my study period of 1st of January 2006 and 31st of December 2016. A total of 10,104 people with a diagnosis of PD (PD-cohort) actively registered in a general practice between the beginning of 2006 and the end of 2016 were identified. There were more males in the PD cohort (60.7% male versus female 39.3%). The PD cohort was matched with 55,664 people without PD (non-PD cohort) for age, gender, calendar year and general practice. The PD cohort had a lower percentage of people in the most deprived quintiles (8.9% vs 10.0%) and a lower percentage of people smoking (6.8% vs 13.1%). In the PD cohort there were 2,031 (20%) deaths while the non-PD cohort had 9,167 (16%) deaths ($p<0.001$; **see Table 5-1**).

Table 5-1. Baseline characteristics for PD and non-PD cohort

Variables	Parkinson's disease cohort *n* = 10,104	Non-Parkinson's disease cohort *n* = 55,664	*p-value
Died *n*	2,031 (20%)	9,167 (16%)	<0.001
Gender *n (%)*			
Men	6,135 (60.72)	33,778 (60.68)	0.945
Women	3,969 (39.28)	21,886 (39.32)	
Age group *n (%)*			
50 to 59	790 (7.82)	4,403 (7.91)	0.705
60 to 69	2,328 (23.04)	12,961 (23.29)	
70 to 79	4,189 (41.46)	23,170 (41.63)	
80 to 89	2,554 (25.28)	13,941 (25.05)	
90 and over	245 (2.40)	1,187 (2.31)	
Townsend score			
1(least deprived)	2,811 (27.82)	13,746 (24.69)	<0.001
2	2,320 (22.96)	12,399 (22.27)	
3	1,901 (18.81)	10,815 (19.43)	
4	1,441 (14.26)	8,728 (15.68)	
5(most deprived)	895 (8.86)	5,565 (10.00)	
Missing	736 (7.28)	4,411 (7.92)	
Smoking status			
Non-smoker	5,500 (54.43)	24,501 (44.02)	<0.001
Ex-smoker	3,126 (30.94)	18,624 (33.46)	
Current smoker	690 (6.83)	7,280 (13.08)	
Missing	788 (7.80)	5,259 (9.45)	

PD-Parkinson's disease. *Chi-squared

Table 5-1 was taken from published manuscript by Okunoye et al in MDS journal and provided in full for reference in Appendix 5.1

In order to examine whether the validated but stringent PD inclusion criteria introduced selection bias and limited the generalisability of the findings, I also examined the differences in demographic characteristics when loosening the inclusion criteria from PD code plus two prescriptions to PD code plus one prescription and PD diagnosis code only. The sociodemographic characteristics were broadly similar across included/excluded groups although the more stringent criteria seemed to include more younger people and men (see **Appendix 5-2: Table 5-1).**

5.8.2 Mortality rates

The overall unadjusted mortality rate in the PD-cohort was 56.06 per 1,000 person-years (95% CI: 53.68 to 58.56) and that in the non-PD cohort was 50.07 per 1,000 person years (95% CI: 49.05 to 51.10) **(See Appendix 5-3: Table 5-2).** Overall mortality rate after adjustment for age, gender, calendar year, social deprivation and smoking, was elevated in the PD-cohort compared to the non-PD cohort (mortality rate ratio 1.14, 95%CI: 1.08 to 1.19) **(see Table 5-2).**

Table 5-2. Overall mortality rates and ratios in the PD and Non-PD cohort

	General population (non-PD cohort)	**Parkinson's disease cohort**	**p-value**
	***n* = 55,664**	***n* = 10,104**	
Deaths, *n*	9,167	2,031	<0.001
PYs, per 1,000	183.09	36.23	
Unadjusted mortality rate, per 1,000 PY (95% CI)	50.07 (49.05 to 51.10)	56.06 (53.68 to 58.56)	
Unadjusted mortality rate ratio	1 (reference)	1.12 (1.07 to 1.17)	<0.001
Age, gender, calendar year, social deprivation, smoking adjusted mortality rate ratio (95% CI)	1 (reference)	1.14 (1.09 to 1.20)	<0.001

PD-Parkinson's disease. PYs-person-years

Table 5-2 was taken from published manuscript by Okunoye et al in MDS journal and provided in full for reference in Appendix 5-1.

5.8.3 Trends in mortality rates over time

The Bayesian Information Criterion (BIC) favoured a linear function for age whereas Akaike's Information Criterion favoured a three-knot spline transformation and I have therefore reported both **(see Figure 5-3).** There was an interaction between PD status and calendar year (p-value for interaction in spline transformed model=0.0005). Adjusted mortality rates in the PD cohort slowly declined over time by around 2% per year or 1.2 per 1000 person-years **(see Table 5-3).** However, in the non-PD cohort mortality rates decreased at a greater rate at 5% per year or 2.4 per 1000 person-years over the time period observed **(see Table 5-3).** Further adjustment for social deprivation and smoking status had no meaningful impact on the estimates (**see Table 5-3 and Appendix 5-4: Figure 5-1).**

There were also strong interactions between PD status and time since diagnosis/index date (p-value for interaction<0.0001). Adjusted mortality rates per 1000 person-years were lower in people with PD than the general population in the year following diagnosis **(see Figure 5-4),** but gradually increased with each year from 43 (95%CI: 38 to 48) in the first year after diagnosis to 75 (95%CI: 64 to 85) at five years after diagnosis **(see Figure 5-4 and Appendix 5-5 and Appendix 5-6**: **Table 5-3 and Table 5-4)**. On the other hand, adjusted mortality rates were decreasing in the non-PD cohort during the follow-up from index date, resulting in a gradually increasing mortality rate ratio with increasing years after diagnosis (mortality rate ratio: in the first year after diagnosis: 0.70 (95%CI: 0.63 to 0.78), in the fifth year: 1.84 (95%CI: 1.59 to

2.12) and tenth year: 2.26 (95%CI: 0.82 to 6.24) (**see Appendix 5-5 and Appendix 5-6**: **Table 5-3 and Table 5-4).**

Time trends were further examined separately by up to four years since diagnosis/index date. There was no strong evidence of non-linearity for calendar year within years since diagnosis/index date and only up to four years were explored due to low number of events. Overall mortality rates were lower in people with PD in the first year and declined at a similar rate to those without PD **(see Table 5-3 and Appendix 5-7: Figure 5-2).** However, the differential decline in mortality rates seen in the most recent years of data was largely driven by the much slower decline in mortality rates for PD patients more than two years after their diagnosis **(see Table 5-3 and Appendix 5-7: Figure 5-2).**

Figure 5-3. Mortality over time: (A) on the linear scale adjusted for age, gender, social deprivation and smoking; (B) on the non-linear scale adjusted for age, gender, social deprivation and smoking.

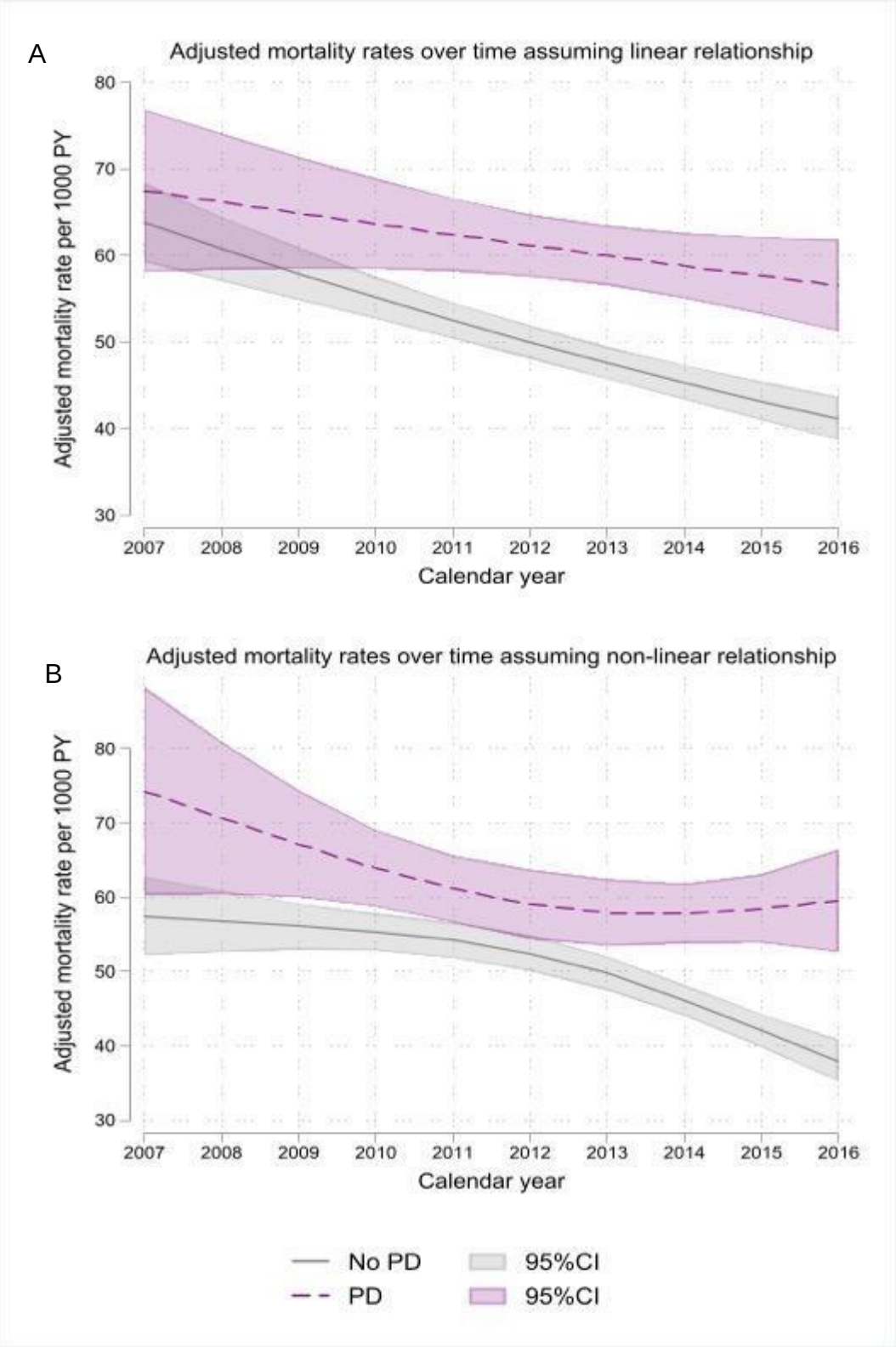


Figure 5-3 was taken from published manuscript by Okunoye et al in MDS journal and provided in full for reference in Appendix 5-1.

Table 5-3. Trends in mortality rates over time (four years following diagnosis of PD/Index date).

	PD cohort trends			**Non-PD cohort trends**			
Adjusted for age, gender, time since diagnosis/index date	Adjusted mortality rate ratio (95% CI)	p-value	Change in adjusted mortality rate (95% CI)	Change in adjusted mortality rate ratio (95% CI)	p-value	Change in adjusted mortality rate (95% CI)	*p-value
Overall time trends 2007-2016	0.98 (0.96 to 1.00)	0.084	-1.19 (-2.54 to 0.16)	0.95 (0.94 to 0.97)	<0.0001	-2.40 (-2.99 to -1.82)	0.0177
0-1 years after diagnosis	0.96 (0.92 to 1.00)	0.033	-1.66 (-3.17 to -0.14)	0.96 (0.95 to 0.98)	<0.0001	-2.35 (-3.32 to -1.38)	
1-2 years after diagnosis	0.98 (0.94 to 1.03)	0.485	-0.78 (-2.97 to 1.41)	0.96 (0.95 to 0.98)	<0.0001	-1.96 (-2.99 to -0.94)	
2-3 years after diagnosis	0.99 (0.94 to 1.04)	0.768	-0.47 (-3.60 to 2.66)	0.94 (0.91 to 0.96)	<0.0001	-3.04 (-4.33 to -1.76)	
3-4 years after diagnosis	0.98 (0.94 to 1.03)	0.520	-1.67 (-6.72 to 3.39)	0.92 (0.89 to 0.96)	<0.0001	-3.54 (-5.16 to -1.92)	
Adjusted for age, gender, time since diagnosis/index date, smoking, social deprivation							
Overall time trends 2007-2016	0.98 (0.96 to 1.00)	0.1060	-1.17 (-2.58 to 0.24)	0.95 (0.94 to 0.97)	<0.0001	-2.32 (-2.89 to -1.74)	0.0202
0-1 years after diagnosis	0.96 (0.92 to 1.00)	0.0360	-1.68 (-3.24 to -0.11)	0.96 (0.95 to 0.98)	<0.0001	-2.26 (-3.21 to -1.31)	
1-2 years after diagnosis	0.98 (0.94 to 1.03)	0.5190	-0.75 (-3.02 to 1.52)	0.96 (0.94 to 0.98)	<0.0001	-1.88 (-2.90 to -0.86)	
2-3 years after diagnosis	0.99 (0.95 to 1.04)	0.8160	-0.39 (-3.65 to 2.88)	0.94 (0.91 to 0.96)	<0.0001	-2.95 (-4.23 to -1.68)	
3-4 years after diagnosis	0.98 (0.91 to 1.05)	0.5570	-1.58 (-6.84 to 3.68)	0.92 (0.89 to 0.96)	<0.0001	-3.44 (-5.05 to -1.84)	

PD-Parkinson's disease. *Wald test for multiplicative interaction between calendar year and year following PD diagnosis/Index date

Figure 5-4. Mortality rates following PD diagnosis/index date adjusted for age, sex, calendar year, social deprivation and smoking.

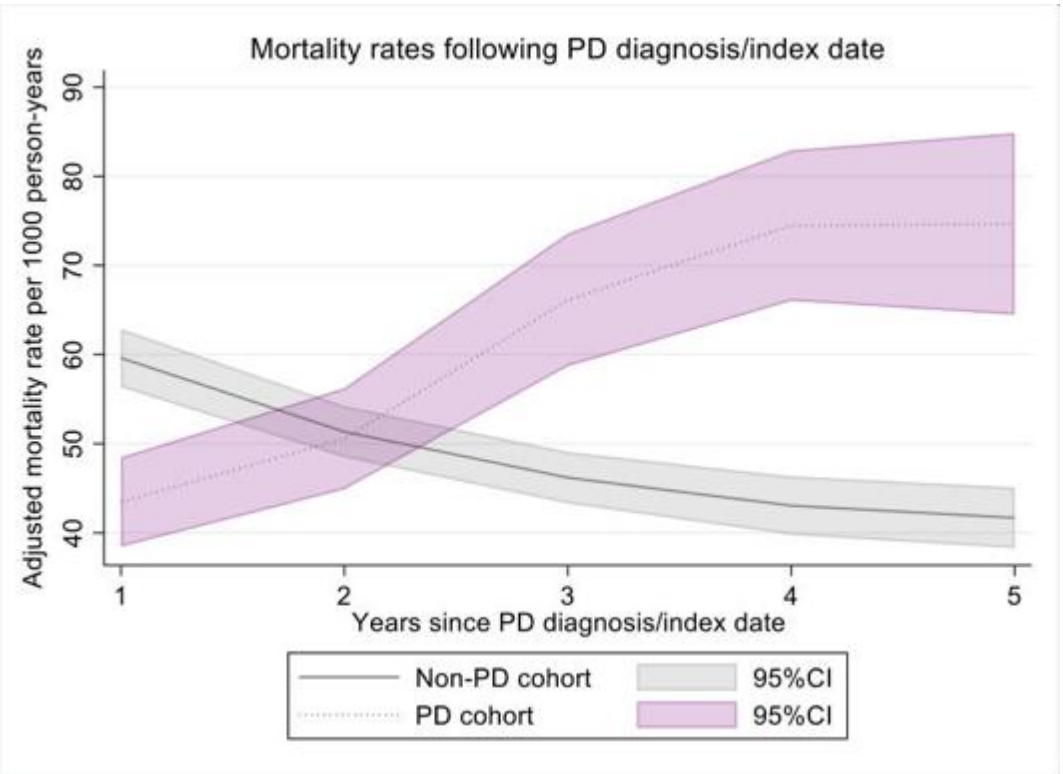


Figure 5-4 was taken from published manuscript by Okunoye et al in MDS journal and provided in full for reference in Appendix 5-1

5.8.4 Accounting for immortal time bias

The period of follow-up during which, by design, death or a study outcome cannot occur is referred to as immortal time (Rothman KJ and Greenland S, 2011). Immortal time arises particularly in pharmacoepidemiologic studies during which follow-up time is accrued when the determination of an individual's treatment status involves a delay or wait period. For example, waiting for a prescription to be dispensed after discharge from hospital when discharge date represents start of follow-up (Sin DD and Tu JV, 2001, Sin DD and McAlister F, 2002, Trojano M et al., 2007, Nichol K et al., 2007, Jackevicius CA et al., 2008, Sheehy O et al., 2008). For this study, waiting for two prescriptions in addition to a first recording of PD diagnosis Read code when PD diagnosis date

represents start of follow-up. This wait or delay period is considered immortal because people in the exposed or treated group must be alive and event free (survive) until the treatment definition is fulfilled. Individuals who take up treatment before an event occurs end up in the untreated or unexposed group. When this period of "immortality" is either misclassified with regards to treatment status or excluded from the analysis (Suissa S, 2007), with immortal time bias, a spurious survival advantage is conferred on the treated group resulting in a bias in favour of the treatment under study (Levesque LE et al., 2010).

In order to account for immortal time bias in this study, I conducted a sensitivity analysis where start of follow-up was moved to the latest date of PD diagnosis using Read code recording or antiparkinsonian drug prescription.[28, 29]

Follow-up started at the end of the immortal period. This made no meaningful difference to the results as shown in **Appendix 5-8: Figure 5-3**. Also, both prescription dates were generally close to the diagnosis date.

5.8.5 Other factors associated with increased mortality rates

Adjusted mortality rates increased with age at a broadly similar rate for the PD and non-PD cohort **(see Table 5-4 and Figure 5-5)** (p-value for interaction in spline transformed model=0.89). Men in both groups had similarly higher adjusted mortality rates in comparison to women (p-value for interaction=0.45) **(see Table 5-4).** In both groups (PD and non-PD cohort), adjusted mortality rates increased similarly with social deprivation (Townsend quintile) and smoking status was also associated with increased mortality. There was some evidence that the differences in mortality rates for the PD and non-PD cohort

were more pronounced in the least deprived areas and in non/former smokers; however, the differences were small **(see Table 5-4 and Appendices 5-9 to 5-11: Table 5-5 to 5-7 and Appendix 5-12: Figure 5-4 and Appendix 5-13: Figure 5-5).**

Table 5-4. Adjusted mortality rates by age group, gender calendar year, social deprivation and smoking

Variables	PD cohort				Non-PD cohort						
	Events	Person-Years (1000)	*Adjusted Mortality rate (95% CI)	p-value	Events	Person-Years (1000)	*Adjusted Mortality rate (95% CI)	p-value	Mortality rate ratio	**p-value	***p-value
Age group											
50 to 59	14	2.09	6.98 (3.0 to 10.97)	<0.001	51	10.63	4.46 (3.30 to 5.62)	<0.001	1.48 (0.80 to 2.76)	0.212	0.474
60 to 69	107	7.74	14.20 (11.30 to 17.09)		521	38.41	13.04 (11.81 to 14.27)		1.08 (0.87 to 1.33)	0.497	
70 to 79	571	14.95	39.57 (35.98 to 43.16)		2,537	74.70	33.53 (31.90 to 35.16)		1.17 (1.07 to 1.28)	0.001	
80 to 89	1,052	10.34	105.75 (98.78 to 112.71)		4,813	53.35	92.91 (89.23 to 96.59)		1.14 (1.07 to 1.22)	<0.001	
>90	287	1.09	285.69 (250.05 to 321.32)		1,245	5.97	223.98 (209.40 to 238.55)		1.28 (1.12 to 1.45)	<0.001	
Gender											
Male	1,288	21.65	65.99 (61.77 to 70.20)	<0.001	5,792	109.53	54.76 (52.41 to 57.12)	<0.001	1.18 (1.11 to 1.25)	<0.001	0.452
Female	743	14.58	51.82 (47.48 to 56.17)		3,375	73.39	44.71 (42.67 to 46.74)		1.14 (1.06 to 1.23)	0.001	
Townsend quintile											
1(least deprived)	510	10.37	55.65 (50.21 to 61.09)	0.0197	1,939	47.19	44.25 (41.53 to 46.98)	<0.001	1.24 (1.13 to 1.37)	<0.001	0.323
2	482	8.54	58.85 (53.02 to 64.68)		2,023	41.57	48.77 (45.90 to 51.64)		1.19 (1.08 to 1.32)	0.001	
3	404	6.69	66.03 (59.30 to 72.75)		1,919	35.70	53.56 (50.29 to 56.83)		1.19 (1.08 to 1.32)	0.001	
4	291	5.05	61.08 (53.75 to 68.40)		1,630	27.52	56.51 (52.48 to 60.54)		1.04 (0.92 to 1.18)	0.497	
5(most deprived)	210	3.0	67.88 (57.89 to 77.87)		1,049	17.67	59.36 (54.55 to 64.17)		1.09 (0.94 to 1.26)	0.246	
No records	134				607						
Smoking Status											
Non-smoker	1035	20.40	53.87 (50.24 to 57.50)	<0.001	3649	82.57	44.21 (42.10 to 46.32)	<0.001	1.18 (1.11 to 1.26)	<0.001	0.086
Ex-smoker	716	10.76	65.14 (59.85 to 70.43)		3450	60.03	54.02 (51.62 to 56.43)		1.19 (1.10 to 1.28)	<0.001	
Current smoker	149	2.50	74.24 (61.70 to 86.78)		1378	23.88	74.74 (69.82 to 79.66)		0.96 (0.80 to 1.13)	0.604	
No records	131				690						

PD-Parkinson's disease. *Adjusted for age, gender calendar year, social deprivation and smoking. **Wald test for categorical variable. ***Wald test for multiplicative interaction. Table 5-4 was taken from published manuscript by Okunoye et al and provided in full for reference in Appendix 5-1.

Figure 5-5. Association between age and mortality by PD showing mortality rates (three-knot cubic spine transformation) adjusted for sex, calendar year, social deprivation and smoking.

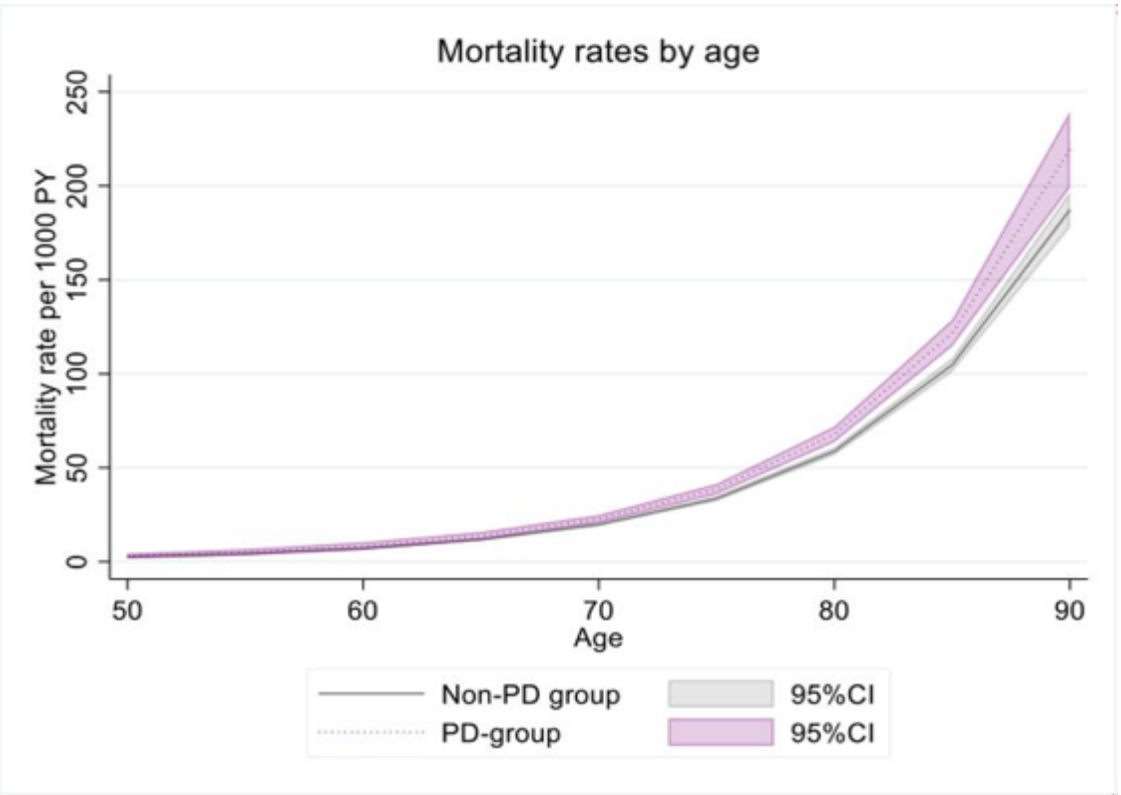


Figure 5-5 was taken from published manuscript by Okunoye et al and provided in full for reference in Appendix 5-1.

5.9 Discussion

5.9.1 Summary of main findings

This study found that the overall mortality rate in people with PD between 2006 and 2016 was slightly higher than those without PD after adjustment for age, gender, calendar year, social deprivation and smoking. Adjusted mortality rates in the PD cohort declined slightly over time by around 2% per year while in the non-PD cohort adjusted mortality rates decreased at a greater rate of 5% per year over the time period observed. Furthermore, adjusted mortality rates were

lower in people with PD than the non-PD cohort in the year following diagnosis**,** but gradually increased with each year following diagnosis from the first year after diagnosis to five years after diagnosis. On the other hand, adjusted mortality rates were decreasing in the non-PD cohort during the follow-up from index date, resulting in a gradually increasing mortality rate ratio with increasing years after diagnosis.

Adjusted mortality rates increased with age at a broadly similar rate for both the PD and non-PD cohort. Men in both groups had similarly higher adjusted mortality rates in comparison to women. There were slight differences in adjusted mortality rates with regards to social deprivation and smoking status in both people with and without PD, but this was not clinically meaningful.

5.9.2 Interpretation of the results within the context of available literature

In this large, population-based cohort study including more than 10,000 people with PD and more than 50,000 controls without PD, the mortality rate ratio in the PD cohort was 1.14 times that of the non-PD cohort indicating a modest increase in mortality. Although at the lower end of previously published mortality results, the mortality rate ratio in this study is within the range reported in literature. In previous research mortality rate ratios in people with PD have been reported to range from 0.9 to 3.8 (Macleod AD et al., 2014). Whilst in the lower range, mortality rate ratio in this study was similar to recent incident clinical and community-based cohort studies which have also reported similar mortality ratios (Duarte J et al., 2013, Macleod AD et al., 2014). Previous population-based or register-based studies (Ebmeier KP et al., 1990, Morens DM et al., 1996, Louis ED et al., 1997, Berger K et al., 2000, de Lau LML et al.,

2005, D'Amelio M et al., 2006, Fink H et al., 2008, Posada IJ et al., 2011) with higher rate ratios have included both prevalent and incident PD cases (de Lau LML et al., 2005), while others included prevalent PD cases which are likely to have higher mortality than newly diagnosed (incident) PD cases (Ebmeier KP et al., 1990, Louis ED et al., 1997, Berger K et al., 2000, Elbaz A et al., 2003, D'Amelio M et al., 2006, Fink H et al., 2008, Posada IJ et al., 2011). Other population-based studies (Rajput AH et al., 1984, Nobrega FT et al., 1997, Williams-Gray CH et al., 2013, Macleod AD et al., 2018) on survival of incident PD patients are limited by small number of cases (Elbaz A et al., 2003, Williams-Gray CH et al., 2013, Macleod AD et al., 2018) and often also included patients with other causes of parkinsonism such as progressive supranuclear palsy, corticobasal degeneration or multiple system atrophy which have been reported to have higher mortality (Herlofson K et al., 2004).

My findings suggested that men with PD had slightly higher mortality in comparison to women with PD, but the differences were small and not different to the non-PD cohort without PD. While previous studies have reported increased mortality in men with PD compared to women with PD (Berger K et al., 2000, Xu J et al., 2014), a Sydney multicentre study showed no difference in the sexes (Hely MA et al., 1999). There are however speculations that female sex hormones (oestrogens) have some neuroprotective effects on neuronal cell death (de Lau LM and Breteler MM, 2006). There are also reports of animal studies which showed that the potential beneficial effects of oestrogens may be due to its antioxidant effects (Saunders-Pullman R, 2003). Other available data are conflicting (Marder K et al., 1998, Benedetti MD et al., 2001, Saunders-Pullman R, 2003, Currie LJ et al., 2004) and further large

observational studies are proposed. I also found no strong differences in mortality rates between people with and without PD with regards to influence of lower socioeconomic status and smoking in this study, both of which are associated with increased mortality (Iacobucci G, 2020).

In comparison to the non-PD cohort, mortality rates were lower in the PD cohort than the non-PD cohort in the year following diagnosis, but it gradually increased in people with PD with longer disease duration, with the excess mortality of people with PD continuing to increase with each year after the diagnosis of PD. The explanation for this could be that patients who present with symptoms leading to diagnosis of PD receive greater medical attention and more investigations at the time of diagnosis, or alternatively due to referral bias where patients with short life expectancy were not referred and did not therefore receive a new PD diagnosis. However, increasing disease duration with advancing disease was associated with higher mortality. This has been reported in recent systematic reviews on mortality in PD in which rate ratios are reported to increase with duration of disease (Macleod AD et al., 2014, Xu J et al., 2014). Also, mortality was reported to increase with disease duration in the Rotterdam study with ratios increasing by 1.03 (95% CI: 0.99 to 1.07) per year (de Lau LML et al., 2005).

Furthermore, increased mortality risk across all categories of disease duration including disease duration below two years (rate ratio 2.00, 95%CI: 1.03 to 3.88) was reported by another study from the USA (Driver JA et al., 2009). The reason for this increasing mortality rate in people with PD with longer disease duration may be related to comorbidities, increasing disease severity or

complications of PD. These will need to be investigated, identified and addressed in order to develop interventions to reduce mortality in PD (Xu J et al., 2014).

In the course of my follow-up period, adjusted mortality rates per 1000 person-years in people with PD declined slightly from 69 (95%CI: 60 to 79) in 2007 to 59 (95%CI: 53 to 64) in 2016. This is in line with previous studies in the UK, which showed a steady decline in mortality in people with PD between 1993 and 2006 (Mylne AQ et al., 2009) as well as earlier time periods (Griffiths C and Rooney C, 2006, Clarke CE, 1993).

On the contrary, a recent study from Northern Italy (Fedeli U and Schievano E, 2017) showed an increasing trend in mortality of people with PD from 1.9% in 2008 to 2.4% in 2015. This study was based on a shorter interval and was limited by mortality data as they included other types of parkinsonism such as multiple system atrophy or corticobasal degeneration (with higher mortality) in their analysis. They also reported that they could not ascertain the specificity of PD in death certificates leading to possible overestimation of PD mortality. Variations in healthcare systems in different countries could also have contributed to differences in PD mortality.

However, mortality rates in the non-PD cohort fell from 63 (95%C:I 58 to 67) in 2007 to 41 (95%CI: 39 to 44) in 2016 over time in line with the previously reported declining mortality rates during that decade. Reports from Office for National Statistics (ONS, 2016) and Public Health England (PHE, 2018) showed a significant decline in age-specific mortality rates in both men and

women over 50 years of age in the UK population between 2006 and 2016. The reason for this reduction in mortality was attributed to falling rates from death due to cardiovascular diseases. As there was a slower decline in mortality rate in the PD cohort, this resulted in an increasing mortality gap between patients with PD and the non-PD cohort over that time period. These data suggest that improvement in mortality in those aged over 50 years in the general population is not seen in the same way in people with PD. It is possible that interventions leading to lower cardiovascular death rates are either not implemented or as effective to the same degree in patients with PD. Alternatively, the process of PD itself is the primary determinant of mortality, particularly in advancing disease, and therefore overshadows improvements in cardiovascular or other health. This interpretation is supported by my sub-analysis of mortality within fixed time periods, which suggested that the increase in the mortality gap is particularly seen with longer disease duration. There are very few comparable studies. In a previous study in Ontario, Canada from 1996 to 2013, the mortality in people with PD declined by 5.5% over 18 years study period (Wong JJ et al., 2019). Whilst this study did not include a control group, precluding a direct comparison with mortality in the general population, they reported that mortality in the general population had previously been found to have decreased by 19% during a similar time period (Wong JJ et al., 2019).

5.10 Strengths and limitations of this study

The major strength of this study is the longitudinal design with a follow-up of ten years using data from The Health Improvement Network. This database has provided data on mortality of people with PD and a comparator group without

PD which were derived from the UK population. An additional strength of this study is that mortality was explored in newly diagnosed PD cases (incident cohort) rather than prevalent cases which may lead to an overestimation of rate ratios (Elbaz A et al., 2003). This suggests that my relatively low mortality rate ratio represents a better estimate for the overall population of patients with PD. In addition, a range of possible demographic and health confounders that could distort the results were taken into consideration while developing a robust statistical approach for analysing mortality data in this cohort study.

There are however limitations with respect to analysis of routine healthcare data. Underdiagnosis of PD cannot be ruled out since registration in the database requires health-seeking behaviour as well as diagnosis and those who do not attend a general practice may be missed. Another limitation in this study is that patients with PD were not examined by the research team, and I have relied on GP codes for clinical diagnoses of PD. This may result in misclassification of PD cases. However, the validity of significant diagnoses in primary care databases is high (Langley TE et al., 2010, Lewis JD et al., 2007), including that for PD with a validity of 90% in GPRD, a similar primary care database (Alonso A et al., 2007) and in most instances, this will be recorded following a diagnosis made in secondary care. Furthermore, the potential for residual confounding cannot be ruled out in any observational study using routine data. In particular I was unable to include factors such as ethnicity or some social factors (for example marital status or having a carer) due to a large amount of missing data. Nevertheless, adjustment for smoking and socioeconomic status as confounders in addition to age- and gender-

standardized mortality rate ratios increased the applicability of the results from this study.

5.11 Summary of the chapter

In this chapter, I used incident cases of PD and a frequency-matched control cohort without PD to explore mortality in PD and showed that mortality rates in people with PD in the UK between 2006 and 2016 were slightly increased in comparison to the general population.

I also examined trends in mortality rates over ten years (2007 to 2016) and mortality rates following diagnosis/index in people with and without PD and showed that mortality was lower than in the general population in the year of diagnosis but increased year on year with advancing disease in people with PD. Over the ten-year period, mortality rates in people without PD declined at a faster rate compared to mortality rates in people with PD leading to a large differential in the most recent year of data (2016). Mortality trends across age, gender, smoking status and social deprivation were broadly similar in people with and without PD. Mortality trends over time and disease duration are similar to previous reports suggesting that progression of PD is associated with increasing mortality and that a decrease in mortality will require treatments to address the underlying disease or associated comorbidities. The importance of the findings from this chapter on clinical, and public health practice and future research directions will be discussed in my final discussion (Chapter 7).

In the next chapter, I describe the incidence of hospital admissions among those with PD in comparison to those without PD in primary care using data from THIN.

Chapter 6 Rate of hospitalisations and underlying reasons among people with Parkinson's disease- Population-based cohort study in UK primary care.

6.1 Chapter overview

In this chapter, I explored hospitalisation among people with Parkinson's disease (PD) compared to frequency-matched people without PD. This chapter builds on my systematic review in Chapter two, where I investigated and synthesised the previous research on rate of hospitalisation and reasons for hospitalisation among people with PD. I also present the potential reasons associated with hospital admissions among people with PD in UK. A paper titled "Rate of hospitalisations and underlying reasons among people with Parkinson's disease- Population-based cohort study in UK primary care" based on these findings has been submitted to Journal of Parkinson's disease and is under review.

6.2 Study background

During the early stages of PD, treatment with antiparkinsonian medications is typically very effective, but as the disease progresses, the disease severity increases, leading to deterioration in their health status and often results in hospitalisation (Woodford H and Walker R, 2005, Chou KL et al., 2011, Arasalingam A and Clarke CE, 2014). Hospitalisations are associated with worse outcomes in people with PD and may lead to worsening of their disease (Zeldenrust F et al., 2020). Patients may suffer a worsening of their motor symptoms, infections, medication errors and higher mortality following surgical procedures (Mueller MC et al., 2009, Gerlach OHH et al., 2012, Gerlach OH et

al., 2013, Harris-Hayes M et al., 2014). Their hospital stay is prolonged (Huse DM et al., 2005) and they are prone to re-admissions (Hassan A et al., 2013). In addition, the cost of hospitalisations is high and likely to increase with aging adult population (Huse DM et al., 2005, Low V et al., 2015, Muzerengi S et al., 2016, Hobson P et al., 2019). There are few studies (Pressley JC et al., 2003, Guttman M et al., 2004) examining the rate of hospitalisation of people with PD. Therefore, identifying rates and causes of hospital admission could help plan for and reduce unwarranted admissions, morbidity and financial burden associated with PD (Guttman M et al., 2003, Kelly B et al., 2016). In the United Kingdom (UK), the rate of hospitalisation among people with PD is hypothesized to be high but there is a dearth of information within the UK setting. I therefore investigated the rate of and reasons for hospitalisation among people with PD in the UK compared to people without PD using a large primary care database.

6.3 Study aim

- To investigate the rate of hospitalisation between 1st of January 2006 and 31st of December 2016 among people with PD in the UK in comparison to people without PD matched by age, sex, time period and general practice using data from a large primary care database-The Health Improvement Network.

6.4 Study objectives

- To estimate the incidence rate of hospital admissions among people with PD in the UK.

- To investigate the association between age, gender, social deprivation and smoking, regional location of general practice and urbanicity on incidence of hospitalisation in PD in the UK.
- To explore the recorded diagnosis that are associated with hospitalisation among people with PD in the UK.

6.5 Methods

6.5.1 Source of data

The Health Improvement Network (THIN) dataset was used for this study **(See Chapter 3,** sections **3.2.5, 3.4 to 3.7)**.

6.5.2 Study population

The same population was used as for Chapter 5 **(see Section 5.5.2)**

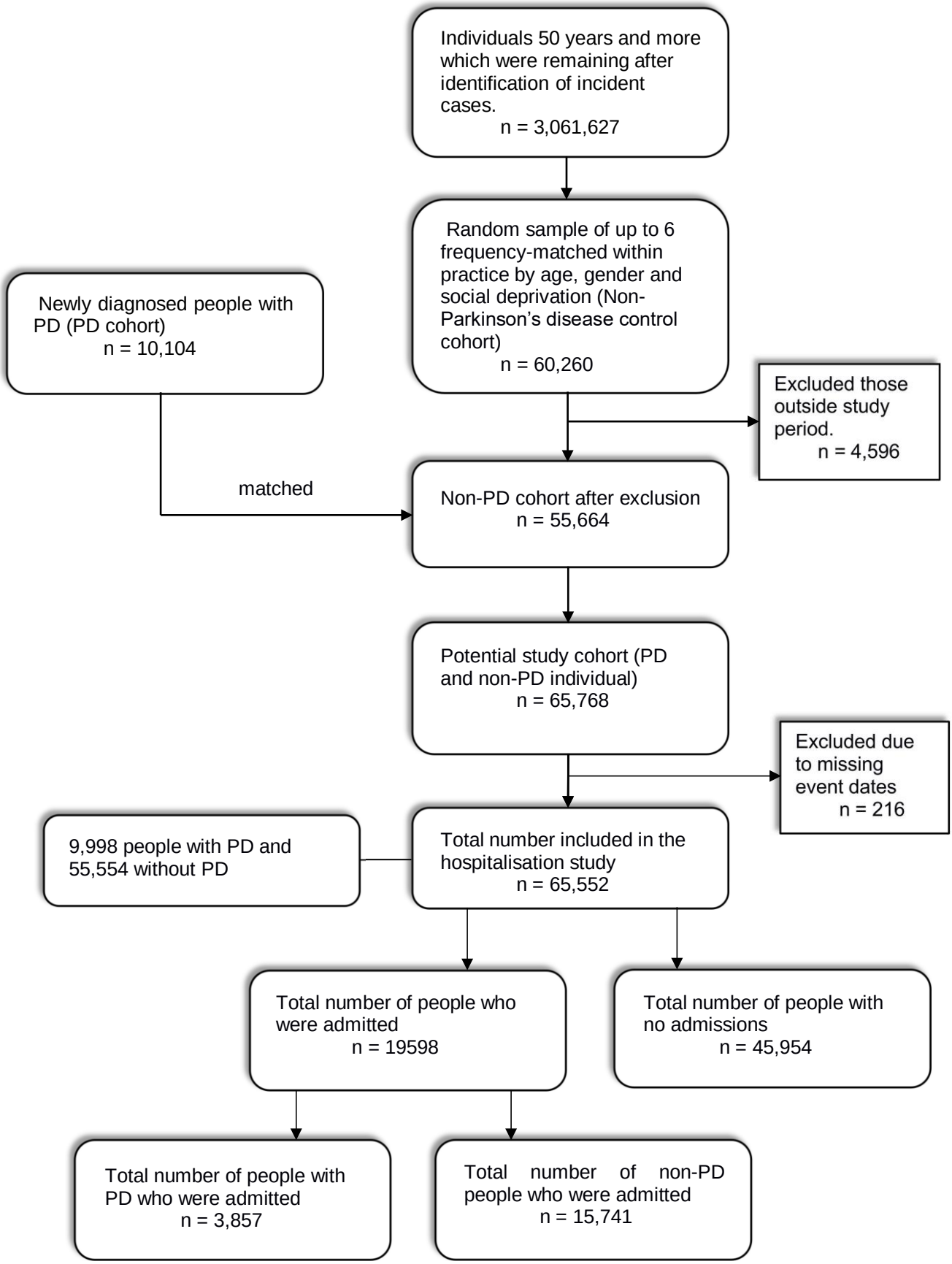
6.5.3 Exclusion criteria

- Same as for Chapter 5 **(see Section 5.5.3)**
- I further excluded 216 individuals with missing admission or discharge date (missing event date).

6.5.4 Study participants

The participants used for this exploratory study consisted of incident cases of Parkinson's disease (PD cohort) and frequency-matched controls without Parkinson's disease (non-PD cohort) identified in Chapter 5 **(see Section 5.5.4 and Figure 5-2)**. Of these cases, those with missing admission/discharge dates (Event date) were excluded **(see Figure 6-1).** This ensured that all participants were able to contribute data during the study period.

Figure 6-1. Process of identifying cohort used for study on hospitalisation in Parkinson's disease (PD).



6.5.5 Study outcomes

My main outcome of interest was hospitalisations which were identified through a computer search by using Read codes for hospital admission. Where the admission codes were not available, discharge codes were used with the assumption that an admission preceded the discharge. These codes (admission/discharge codes) were then applied to the medical records for each individual to get an event (admission/discharge). In order to avoid counting the same admission/discharge more than once, admission/discharge codes within twenty-one days of a previous admission/discharge code were considered as the same admission as the mean length of stay in hospital from available literature was 17 days (SD 7).

Diagnoses associated with admissions were identified using Read code entries from date of diagnosis up to 28 days following discharge (allowing time for discharge summaries to get to the GP practice from secondary care)(QuintilesIMS, 2017) after a hospital admission.

Common reasons for hospitalisation among people with PD were previously identified through a systematic review and meta-analysis I conducted (Okunoye O et al., 2020) **(see Chapter 2)**. These reasons for hospitalisation among people with PD included infections (mainly chest, urinary tract, skin and subcutaneous tissue infections), falls, fractures, cardiovascular comorbidities (hypertension and myocardial infarction), neuropsychiatric problems (psychosis and hallucinations) dementia, and gastrointestinal complications (dysphagia, constipation, nausea and vomiting), postural hypotension, electrolyte problems, surgical procedures and where PD was recorded as a reason. Read code lists

for admission/discharge and those for reasons for admission were developed using previously published methods (Dave S and Petersen I, 2009), and applied to the medical records for each study participant with data on admission/discharge. A combination of Read codes and blood pressure readings were used to define those with hypertension **(see Chapter 5: section 5.5.4.3 and Appendix 6-1).**

6.5.6 Covariates

Data on demographics and social deprivation were collected. Townsend quintile was used to measure social deprivation. This is a measure derived from a combination of area postcode linked to individuals' occupation, car-ownership, unemployment and household overcrowding. It is categorised into quintiles from 1 (least deprived) to 5 (most deprived). Information on urban-rural living is provided through the Government classification system (Classification RU, 2016). The boundaries of the former strategic health authorities based in England are linked to UK geographic regions **(see Chapter 3).**

6.6 Statistical analysis

Chi-squared test was used to compare the baseline characteristics of the study cohort. Incidence rates of hospitalisation per 1,000 person years with 95% CI were calculated. Data were split by one-year intervals and calendar year was used as a continuous variable with age taken as the timescale. Age was split by ten-year intervals and used as a categorical variable. In order to estimate incidence rate ratios and marginal effects adjusted for age, calendar year and

other covariates, multivariable Poisson regression analyses were employed. The marginal effect which is an estimation of how much the incidence rate is predicted to change for every unit of change in an exposure variable is useful for visualizing effects of interactions that are difficult to interpret directly from the model coefficients. The marginal effects (adjusted incidence rates) for fixed values of calendar year were calculated while holding all other variables in the model at their observed values. In order to estimate robust standard errors, the delta method was used with practice identifiers to account for the effects of clustering of observations within general practices. I investigated overdispersion by running and comparing the outputs of negative binomial models. Incidence rate ratios (after the regression analyses) for the categorical variables were computed. The Wald test was used to calculate p-values for multiplicative interaction terms and categorical variables.

6.7 Ethics and data permissions

See Chapter 3 (Section 3.4) and **Appendix 3-1.**

6.8 Results

6.8.1 Demographic characteristics

The study cohort consisted of 9,998 people with PD and 55,554 control without PD matched within practice on age, gender and calendar year. These were all actively registered within a general practice for at least six months between the 1st of January 2006 and 31st of December 2016. Mean age of the study population was 74 years (SD 8.18). The PD cohort had more males (60.8%

males vs 39.3% females). Median follow-up period for both PD and non-PD cohort was 5.10 years (IQR 4.60 to 5.80). Median follow up time for those 50 to 69 years was 5.08 years (IQR 4.56 to 5.75) and those 70 years and over was 6.42 years (IQR 6.08 to 6.84).

A total of 56,391 hospital admissions were identified, 12,452 in the PD cohort and 43,939 in the non-PD control cohort. These admissions were from 19,598 individuals: 3,857 patients (39% of those with PD) were those with PD and 15,741 patients (28% of those without PD) were those without PD from the control cohort. The mean number of admissions among those admitted for the PD cohort was 3 (SD 5) and for the non-PD control cohort was 2 (SD 3). The median number of admissions among those who were admitted was 2 for both groups. **(see Table 6-1).**

Potential reasons for admission were identified for 3,493 of the 3,857 people with PD and 11,746 the 15,741 without PD **(see Table 6-4).**

Table 6-1. Cohort characteristics.

Characteristics	**PD cohort (*n* = 9,998)**	**Non-PD cohort (*n* = 55,554)**	***p-value**
Number of people admitted at least once *n*	3,857 (39%)	15,741 (28%)	<0.001
Median number of admissions among those admitted *n (IQR)*	2 (1 to 4)	2 (1 to 3)	
Gender *n (%)*			
Men	6,093 (60.94)	33,778 (60.68)	0.624
Women	3,905 (39.06)	21,886 (39.32)	
Age group *n (%)*			
50 to 59 years	786 (7.86)	4,403 (7.91)	0.787
60 to 69 years	2,320 (23.21)	12,961 (23.29)	
70 to 79 years	4,149 (41.50)	23,170 (41.63)	
80 to 89 years	2,507 (25.08)	13,941 (25.05)	
90 years and over	236 (2.35)	1,189 (2.31)	
Townsend score *n (%)*			
1(least deprived)	2,791 (27.92)	13,746 (24.69)	<0.001
2	2,300 (23.00)	12,399 (22.27)	
3	1,872 (18.72)	10,815 (19.43)	
4	1,421(14.21)	8,728 (15.68)	
5(most deprived)	882 (8.82)	5,565 (10.00)	
Missing	732 (7.32)	4,411 (7.92)	
Urbanicity *n (%)*			
Urban	5,785 (57.86)	31,878 (57.27)	0.201
Town	1,024 (10.24)	5,632 (10.12)	
Rural	625 (6.25)	3,336 (5.99)	
No records	2,564 (25.65)	14,818 (26.62)	
UK Countries *n (%)*			
England	38,837 (69.77)	7,006 (70.07)	0.918
Northern Ireland	2,804 (5.04)	492 (4.92)	
Wales	8,502 (15.27)	1,510 (15.10)	
Scotland	5,521 (9.92)	990 (9.90)	
Smoking status *n (%)*			
Non-smoker	5,444 (54.45)	24,514 (44.04)	<0.001
Ex-smoker	3,091 (30.92)	18,624 (33.46)	
Current smoker	685 (6.85)	7,280 (13.06)	
Missing	778 (7.78)	5,259 (9.45)	

PD-Parkinson's disease. *Chi-squared test

6.8.2 Incidence rate of hospital admissions

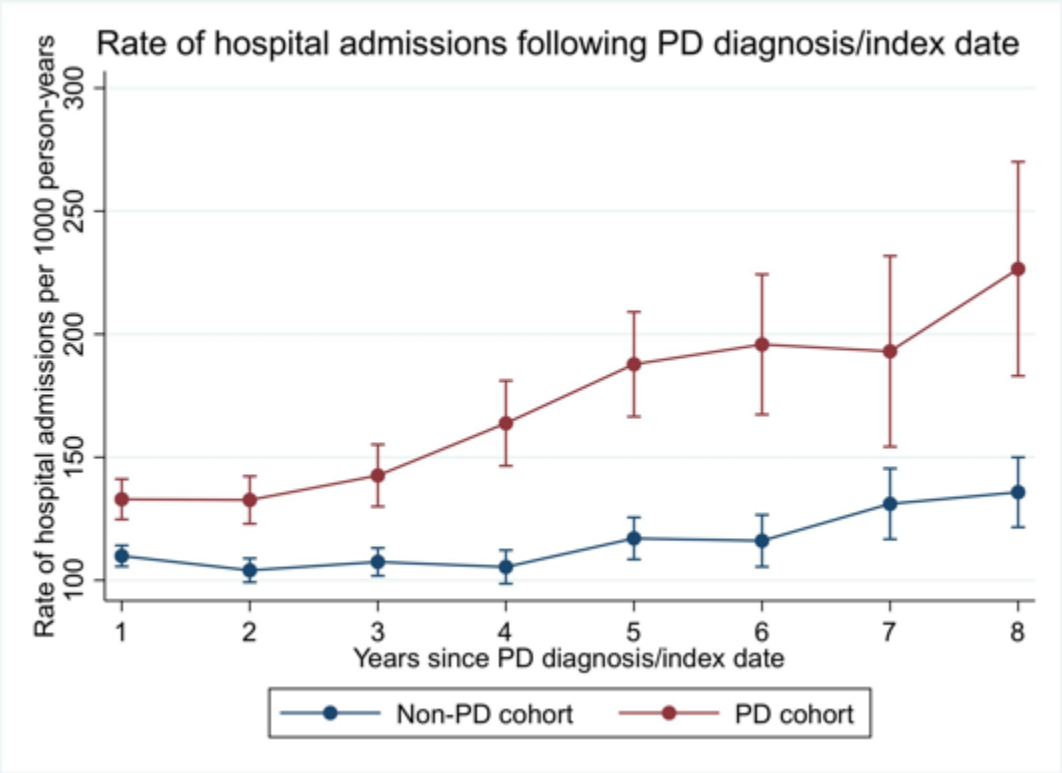
The overall unadjusted incidence rate of hospitalisation among PD cohort was 146.15 per 1,000 person-years (95%CI: 141.61 to 150.84) and 108.98 per 1,000 person-years (95%CI: 107.29 to 110.70) in the non-PD cohort **(see Appendix 6-2: Table 6-5).** After adjusting for age, calendar year, gender, geographic location of practice, urbanicity, social deprivation and smoking status, rate of hospital admissions among patients with PD was higher than the non-PD cohort (incidence rate ratio 1.33, 95%CI: 1.29 to 1.37) **(see Table 6-2).** Rate of hospital admissions increased with longer time from diagnosis or index date **(see Figure 6-2 and Appendix 6-3: Table 6-6).**

Table 6-2. Overall Incidence rates and ratios of hospital admissions

Variables	**PD cohort** ***n*** **= 9998**	**Non-PD cohort** ***n*** **= 55,554**	**p-value**
Number admitted	3,857 (39%)	15,741 (28%)	<0.001
Person-years, per 1,000	26.39	144.43	
Unadjusted incidence rate, per 1,000 PY (95%CI)	146.15 (141.61 to 150.84)	108.98 (107.29 to 110.70)	
Unadjusted incidence rate ratio	1.34(1.30 to 1.39)	1 (reference)	<0.001
Incidence rate ratio (95%CI) adjusted for age, gender and calendar year	1.32 (1.28 to 1.37)	1 (reference)	<0.001
Incidence rate ratio (95%CI) adjusted for age, gender, calendar year and social deprivation.	1.32 (1.28 to 1.37)	1 (reference)	<0.001
Incidence rate ratio (95%CI) adjusted age, gender, calendar year, social deprivation and smoking	1.33 (1.28 to 1.37)	1 (reference)	<0.001
Incidence rate ratio (95%CI) adjusted age, gender, calendar year social deprivation, smoking, urban-rural and UK countries.	1.33 (1.28 to 1.37)	1 (reference)	<0.001

PD-Parkinson's disease

Figure 6-2. Association between disease duration and incidence rate of hospital admissions for people with Parkinson's disease (PD) and the non-Parkinson's disease cohort.



6.8.3 Factors associated with increased hospital admissions

Among the PD cohort, after adjusting for age, gender, calendar year, social deprivation, smoking, urbanicity and geographic location of practice, adjusted incidence rates for hospital admissions in the younger age groups (50 to 59 and 60 to 69) were approximately 40% higher than those in the non-PD cohort in the same age groups. Adjusted incidence rates of hospital admission appeared to gradually level up in the older age groups: the adjusted incidence rate for age group 50 to 59 in the PD cohort versus non-PD cohort was 108.95 per 1,000 person-years (95%CI: 92.39 to 125.50) versus 60.28 per 1,000 person-years (95%CI: 54.70 to 65.86) whereas the adjusted incidence rates for age group >90 for PD cohort versus non-PD cohort was 204.09 per 1,000

person-years (95%CI: 171.07 to 237.11) versus 192.59 per 1,000 person-years (95%CI: 175.60 to 209.57) **(see Figure 6-3 and Table 6-3).**

There was no relationship between rates of hospital admissions between people with and without PD regarding urbanicity, UK countries and social deprivation **(see Table 6-3 and Appendix 6-4: Table 6-7 to Appendix 6-6: Table 6-9).**

Figure 6-3. Association between age group and incidence rate of hospital admissions for people with Parkinson's disease (PD) and the non-Parkinson's disease cohort.

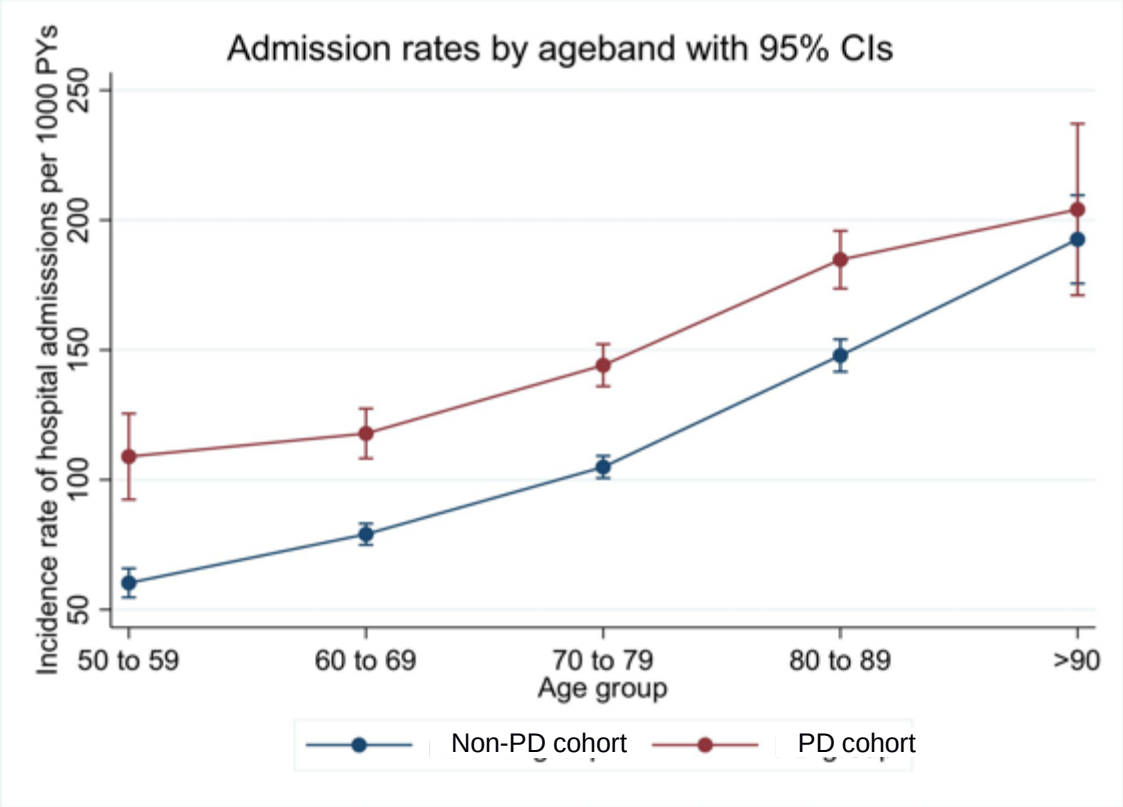


Table 6-3. Adjusted incidence rates and ratios of hospital admissions by age group, gender, calendar year, social deprivation, urban-rural, UK countries and smoking.

Variables	PD cohort				Non-PD cohort						
	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	p-value	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	p-value	Incidence rate ratio	**p-value	***p-value
Age group											
50 to 59	183	1.70	108.95 (92.39 to 125.50)	<0.001	574	9.49	60.28 (54.70 to 65.86)	<0.001	1.79 (1.52 to 2.11)	<0.001	<0.001
60 to 69	692	5.95	117.82 (108.22 to 127.42)		2546	32.30	79.03 (74.93 to 83.14)		1.49 (1.37 to 1.61)	<0.001	
70 to 79	1570	11.03	144.10 (135.99 to 152.22)		6195	59.39	104.91 (100.63 to 109.20)		1.37 (1.30 to 1.44)	<0.001	
80 to 89	1273	7.02	184.76 (173.64 to 195.87)		5680	39.22	147.86 (141.63 to 154.09)		1.25 (1.17 to 1.32)	<0.001	
>90	139	0.69	204.09 (171.07 to 237.11)		746	4.04	192.59 (175.60 to 209.57)		1.06 (0.89 to 1.26)	0.492	
Gender											
Male	2343	15.89	150.21 (142.78 to 157.64)	0.3706	9533	86.54	112.39 (108.15 to 116.63)	0.0457	1.34 (1.29 to 1.40)	<0.001	0.938
Female	1514	10.50	147.21 (138.70 to 155.72)		6208	57.89	108.31 (103.82 to 112.80)		1.35 (1.28 to 1.42)	<0.001	
Townsend quintile											
1(least deprived)	1089	7.57	144.33 (133.44 to 155.22)	0.6200	3938	37.03	107.16 (101.72 to 112.61)	0.0110	1.35 (1.27 to 1.44)	<0.001	0.076
2	924	6.16	154. 59 (143.78 to 165.40)		3471	32.03	107.33 (102.17 to 112.49)		1.43 (1.33 to 1.54)	<0.001	
3	702	4.87	148.03 (136.43 to 159.63)		3066	28.13	110.90 (105.13 to 116.67)		1.34 (1.24 to 1.45)	<0.001	
4	532	3.73	146.06 (133.32 to 158.79)		2511	21.67	117.0 (110.97 to 123.02)		1.25 (1.14 to 1.36)	<0.001	
5(most deprived)	340	2.18	156.18 (139.42 to 172.94)		1547	14.24	110.62 (103.55 to 117.69)		1.41 (1.27 to 1.57)	<0.001	
No records	270				1208						
Urban-rural											
Urban	2269	14.86	149.45 (137.57 to 161.33)	<0.001	9312	81.38	111.31 (105.31 to 117.31)	0.8632	1.34 (1.28 to 1.41)	<0.001	0.952
Town	416	2.73	149.31 (131.76 to 166.87)		1641	14.67	110.11 (101.05 to 119.18)		1.36 (1.24 to 1.49)	<0.001	
Rural	249	1.69	147.45 (126.79 to 168.10)		948	8.38	114.42 (104.22 to 124.61)		1.31 (1.16 to 1.48)	<0.001	
No records	923				3840						
UK Countries											
England	2736	17.73	155.22 (144.46 to 165.98)	<0.001	11,276	97.17	115.90 (110.50 to 121.31)	<0.001	1.33 (1.28 to 1.39)	<0.001	0.141

Northern Ireland	248	1.25	211.0 (159.79 to 262.20)	988	7.76	140.92 (117.53 to 164.30)	1.55 (1.37 to 1.74)	<0.001
Wales	471	4.48	107.23 (81.70 to 132.75)	1893	24.19	81.69 (67.14 to 96.23)	1.34 (1.23 to 1.45)	<0.001
Scotland	402	2.92	142.06 (127.0 to 157.13)	1584	15.32	106.04 (97.16 to 114.92)	1.33 (1.22 to 1.45)	<0.001

*Adjusted for age, gender, calendar year, social deprivation, urban-rural, UK countries and smoking. **Wald test for categorical variables. ***Wald test for interaction terms. PD-Parkinson's disease.

6.8.4 Reasons for hospital admissions

Whilst the most common potential reasons for hospital admissions in both groups were falls and fractures, infections (mainly chest, urinary tract and skin and subcutaneous tissue infections), gastrointestinal complications (dysphagia, constipation, nausea and vomiting) and dementia, these were all more common in patients with PD, as were postural hypotension, electrolyte disturbances, stroke, surgical procedures and psychosis/hallucinations, the latter being seven times more common in the PD population. In addition, patients with PD were admitted due to their PD only (i.e the potential reason for admission recorded was PD). On the other hand, hypertension was slightly less common reason for admission in those with PD than those without PD. There were no differences in the rates of admissions for myocardial infarction/ischaemic heart disease, congestive heart failure, cancer and other cardiovascular diseases between the PD and non-PD cohort **(see Table 6-4).**

Table 6-4. Reasons for hospital admissions among those admitted.

	PD cohort			Non-PD cohort				
Reasons for hospital admission	Number admitted	% admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Number admitted	% admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Incidence rate ratio (95% Confidence Interval)	*p-value
Neuropsychiatric complications (psychosis and hallucinations)	138	3.58	5.23 (4.43 to 6.18)	97	0.62	0.67 (0.55 to 0.82)	7.58 (5.82 to 9.89)	<0.001
Dementia	282	4.15	15.73 (14.28 to 17.31)	668	1.18	4.50 (4.17 to 4.86)	3.49 (3.06 to 3.99)	<0.001
Myocardial infarction/Ischaemic heart disease	86	2.23	3.26 (2.64 to 4.03)	569	3.61	3.90 (3.59 to 4.23)	0.80 (0.64 to 1.01)	0.057
Congestive heart failure	95	2.46	3.60 (2.94 to 4.40)	649	4.12	3.60 (2.94 to 4.40)	0.80 (0.63 to 1.00)	0.052
Stroke	168	4.36	6.33 (5.44 to 7.36)	698	4.43	4.80 (4.46 to 5.18)	1.30 (1.11 to 1.52)	0.001
Hypertension	92	2.39	3.49 (2.84 to 4.28)	639	4.06	4.37 (4.04 to 4.72)	0.79 (0.63 to 1.00)	0.038
Gastrointestinal complications	417	10.81	15.80 (14.36 to 17.39)	1,330	8.45	9.21 (8.73 to 9.72)	1.69 (1.51 to 1.90)	<0.001
Falls	517	13.40	19.59 (17.97 to 21.35)	1,206	7.66	8.35 (7.89 to 8.83)	2.33 (2.10 to 2.59)	<0.001
Fractures	316	8.19	11.94 (10.69 to 13.33)	734	4.66	5.02 (4.67 to 5.41)	2.34 (2.03 to 2.69)	<0.001
Infections	444	11.51	16.82 (15.33 to 18.46)	1,623	10.31	11.23 (10.70 to 11.79)	1.50 (1.34 to 1.67)	<0.001
Recorded as cardiovascular causes	212	5.50	8.00 (6.99 to 9.15)	1,052	6.68	7.23 (6.81 to 7.69)	1.08 (0.93 to 1.26)	0.323
cancer	250	6.48	9.47 (8.37 to 10.72)	1406	8.93	9.69 (9.20 to 10.21)	0.97 (0.85 to 1.11)	0.665
Postural hypotension	229	2.29	8.68 (7.62 to 9.88)	341	0.61	2.34 (2.10 to 2.60)	3.60 (3.05 to 4.26)	<0.001
Electrolyte imbalance	79	0.79	2.99 (2.40 to 3.73)	295	0.53	2.04 (1.82 to 2.29)	1.48 (1.15 to 1.90)	0.003
Parkinson's disease	177	4.59		NA	NA	NA	NA	NA
Surgical causes	273	2.73	10.31 (9.15 to 11.61)	1,107	1.99	7.66 (7.22 to 8.12)	1.30 (1.13 to 1.49)	<0.001
Not identified	364			3995				

PD-Parkinson's disease. *Adjusted for age, gender, calendar year, social deprivation and smoking.

6.8.5 Reasons for hospital admissions stratified by age group

Since younger patients may have different reasons for admissions, I stratified reasons for admission by age groups: 50 to 69 years and 70 years and more.

In those with PD in the younger age group (50 to 69 years), gastrointestinal complications, infections, falls, fractures, postural hypotension, surgical procedures, electrolyte imbalance, psychosis/hallucinations were more common reasons for admission than matched controls in same age group. There was no difference in rates of hospital admissions for myocardial infarction/ischaemic heart disease, congestive heart failure, hypertension, stroke and cancer **(see Table 6-5).**

In the older PD population (70 years and more), falls/fractures, infections, gastrointestinal problems, postural hypotension, surgical procedures, stroke and psychosis/hallucinations were more common than matched controls, whilst myocardial infarction/ischaemic heart, congestive heart failure and hypertension were less common reasons for admission in the older people with PD than those without PD in the same age group, and there was no difference in the rate of admission for cancer **(see Table 6-6).**

Table 6-5. Reasons for hospital admissions among the admitted cohort who are in the younger age group (50 to 59 and 60 to 69 years)

	PD cohort		**Non-PD cohort**			
Reasons for hospital admission	Number admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Number admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Incidence rate ratio (95% Confidence Interval)	*p-value
Neuropsychiatric complications (psychosis and hallucinations)	45	4.61 (3.44 to 6.18)	12	0.23 (0.13 to 0.40)	19.46 (10.65 to 35.56)	<0.001
Myocardial infarction/Ischaemic heart disease	30	3.07 (2.15 to 4.40)	157	3.00 (2.56 to 3.50)	0.96 (0.65 to 1.43)	0.851
Dementia	102	10.45 (8.61 to 12.69)	48	0.92 (0.69 to 1.22)	11.41 (7.96 to 16.35)	<0.001
Congestive heart failure	19	1.95 (1.24 to 3.05)	102	1.95 (1.60 to 2.36)	1.00 (0.60 to 1.65)	0.986
Stroke	31	3.18 (2.23 to 4.52)	132	2.50 (2.10 to 2.97)	1.28 (0.84 to 1.93)	0.245
Hypertension	42	4.30 (3.18 to 5.83)	226	4.31 (3.79 to 4.91)	0.94 (0.68 to 1.32)	0.733
Gastrointestinal complications (dysphagia, constipation, nausea and vomiting)	140	14.35 (12.16 to 16.93)	285	5.44 (4.84 to 6.11)	2.57 (2.07 to 3.21)	<0.001
Falls	109	11.17 (9.26 to 13.48)	174	3.32 (2.86 to 3.85)	3.28 (2.54 to 4.24)	<0.001
Fractures	89	9.02 (7.32 to 11.12)	139	2.60 (2.19 to 3.07)	3.32 (2.52 to 4.37)	<0.001
Infections	125	12.81 (10.75 to 15.27)	386	7.35 (6.65 to 8.12)	1.74 (1.41 to 2.13)	<0.001
Recorded as cardiovascular causes	56	5.74 (4.42 to 7.46)	273	5.21 (4.63 to 5.87)	1.06 (0.78 to 1.43)	0.711
cancer	78	7.99 (6.40 to 9.98)	369	7.04 (6.36 to 7.80)	1.10 (0.86 to 1.41)	0.449
Postural hypotension	67	6.87 (5.41 to 8.73)	56	1.05 (0.81 to 1.37)	6.32 (4.36 to 9.15)	<0.001
Electrolyte imbalance	21	2.15 (1.40 to 3.30)	49	0.94 (0.71 to 1.24)	2.31 (1.39 to 3.84)	0.001
Parkinson's disease	44	4.00 (2.92 to 5.47)	NA	NA	NA	NA
Surgical causes	85	8.71(7.04 to 10.78)	320	6.11 (5.48 to 6.82)	1.37 (1.05 to 1.78)	0.018
Not identified	177		1416			

PD-Parkinson's disease. *Adjusted for age, gender, calendar year, social deprivation and smoking.

Table 6-6. Reasons for hospital admissions among the admitted cohort who are in the older age group (70 years and more)

	PD cohort		Non-PD cohort			
Reasons for hospital admission	Number admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Number admitted	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Incidence rate ratio (95% Confidence Interval)	*p-value
Neuropsychiatric complications (psychosis and hallucinations)	93	5.59 (4.56 to 6.85)	85	0.92 (0.75 to 1.14)	5.91 (4.37 to 8.01)	<0.001
Myocardial infarction/Ischaemic heart disease	56	3.37 (2.59 to 4.37)	412	4.41 (4.00 to 4.86)	0.74 (0.56 to 1.00)	0.036
Dementia	180	18.82 (16.84 to 21.02)	620	6.54 (6.04 to 7.08)	2.83 (2.45 to 3.28)	<0.001
Congestive heart failure	76	4.57 (3.65 to 5.72)	547	5.93 (5.45 to 6.45)	0.76 (0.59 to 1.00)	0.038
Stroke	137	8.18 (6.91 to 9.67)	566	6.12 (5.63 to 6.64)	1.31 (1.10 to 1.57)	0.003
Hypertension	50	3.01 (2.28 to 3.97)	413	4.40 (4.00 to 4.85)	0.68 (0.50 to 0.93)	0.015
Gastrointestinal complications (dysphagia, constipation, nausea and vomiting)	277	16.65 (14.80 to 18.73)	1,045	11.35 (10.68 to 12.06)	1.45 (1.27 to 1.66)	<0.001
Falls	408	24.53 (22.26 to 27.03)	1,032	11.21 (10.55 to 11.92)	2.17 (1.94 to 2.44)	<0.001
Fractures	227	13.65 (11.98 to 15.54)	595	6.41 (5.91 to 6.95)	2.11 (1.79 to 2.48)	<0.001
Infections	319	19.18 (17.18 to 21.40)	1,237	13.44 (12.71 to 14.21)	1.42 (1.26 to 1.61)	<0.001
Recorded as cardiovascular causes	156	9.32 (7.96 to 10.91)	779	8.39 (7.82 to 9.00)	1.09 (0.91 to 1.30)	0.338
cancer	172	10.34 (8.90 to 12.01)	1,037	11.20 (10.54 to 11.90)	0.92 (0.78 to 1.08)	0.312
Postural hypotension	162	9.74 (8.35 to 11.36)	285	3.07 (2.74 to 3.45)	3.08 (2.54 to 3.73)	<0.001
Electrolyte imbalance	58	3.49 (2.70 to 4.51)	246	2.67 (2.36 to 3.03)	1.31 (0.97 to 1.76)	0.078
Parkinson's disease	133		NA	NA	NA	NA
Surgical causes	188	11.24 (9.74 to 12.97)	787	8.54 (7.96 to 9.16)	1.27 (1.09 to 1.49)	0.003
Not identified	187		2579			

PD-Parkinson's disease. *Adjusted for age, gender, calendar year, social deprivation and smoking.

6.9 Discussion

6.9.1 Summary of main findings

In this large exploratory population-based cohort study, I demonstrate that people with PD were 1.33 times more likely to be hospitalised than non-PD cohort who have been matched by age, gender, calendar year and practice. Also adjusted rates of hospitalisation rose with increased disease duration and so did incidence rate ratio of admissions, resulting in a gap in admissions between the PD and the non-PD cohort with longer disease duration. Although admissions rates were higher in the older people with PD than those without PD, the difference in admission rates between those with PD versus those without PD was greater in the younger age group with PD. There were no differences in rates of admission between males and females in people with and without PD. There were no associations between rates of hospital admissions between people with and without PD regarding social deprivation, urbanicity, geographic location of practice (country) and smoking.

The most common potential reasons recorded for hospitalisation among people with PD were falls/fractures, infections (mainly chest, urinary tract and skin and subcutaneous tissue infections), gastrointestinal complications (mainly constipation and dysphagia, nausea and vomiting), dementia, psychosis and hallucinations, postural hypotension, electrolyte disturbances, stroke and surgical reasons. There were no differences in the rates of admissions due to myocardial infarction/ischaemic heart disease, congestive heart failure, cancer and other cardiovascular diseases between people with and without PD.

Admissions due to hypertension were slightly lower in patients with PD than in matched controls.

6.9.2 Interpretation of the results within the context of available literature

6.9.2.1 Rate of hospital admissions

The rate of hospital admissions among people with PD in UK primary care was 1.33 times higher than the matched control population and was increased from the year after diagnosis but rose with increasing duration of the disease. Whilst there are no comparable studies in the UK population, this rate ratio of hospitalisation is comparable, albeit slightly lower, to the results of previous studies where people with Parkinsonism were reported to be 1.50 (USA)(Pressley JC et al., 2003) and 1.44 (Canada)(Guttman M et al., 2004) times more likely to be admitted to the hospital compared to controls. My slightly lower rates could be explained by the fact that these studies were conducted in prevalence cohorts rather than incident cohorts which, whilst not reported, are likely to have had longer average disease durations. In addition, they included patients with parkinsonism, including atypical parkinsonism (multiple system atrophy and corticobasal degeneration) which have higher morbidity and worse prognosis. Furthermore, differences in healthcare systems, for example the predominantly outpatient-based management and lower number of hospital beds per population in the UK, could have contributed to lower rate ratio for hospitalisation of people with PD in the UK (Imison C et al., 2012).

Similar to previous studies (Romero J et al., 2012, Gil-Prieto R et al., 2016), rates of hospital admissions increased with increasing age in both PD and non-

PD cohort, with people in the PD cohort having higher rates of admissions. The difference in admission rates were however most marked in the younger age groups of people with PD but gradually levelled off in the older age groups. Nevertheless, patients in the older age group were still being admitted more frequently than patients with PD in the younger age group.

Contrary to a previous study which reported higher admission rates in men, I found no difference in rates of admission between males and females in people with and without PD (Gil-Prieto R et al., 2016). Reports of gender differences in PD is conflicting. Whilst some studies have reported increased frequency of pain, postural instability, urinary incontinence and urinary infection (which could lead to increased hospitalisations) in females (Rajput AH et al., 1984, Scott B et al., 2000, Ehrt U et al., 2007), others have reported no gender differences in these clinical features (Scott B et al., 2000). Gender differences in PD have been attributed to differences in risk, or protective factors in men and women with PD which are related to their epidemiological, clinical and prognostic differences (Savica R et al., 2013). There are reports of direct hormonal and genetic mechanisms which are protective in women compared to men. Most studies which have explored the protective effect of oestrogen in women were animal studies (Dluzen D, 1997, Miller DB et al., 1998, Callier S et al., 2000, Gao X and Dluzen D, 2001, Sawada H and Shimohama S, 2003, Gillies GE et al., 2004, Rocca W et al., 2008) with conflicting reports and require further investigation (Marder K et al., 1998, Benedetti MD et al., 2001, Currie LJ et al., 2004).

There were no associations between rates of hospital admissions between people with and without PD regarding urbanicity, UK countries and social deprivation in my study, though there are reports of strong association between rurality and hospital admissions. There are lower rates of admissions in the rural populations due to increased distance to the hospitals (Cook P and Porter L, 1998). In addition, recent studies have also found that greater distance from hospital correlated with lower rates of admission and these were likely rural populations (Bankart MJ et al., 2011, Imison C et al., 2012).

6.9.2.2 Reasons for hospital admissions

The main potential causes for admissions overlapped with those of the matched non-PD population, including falls and fractures, infections and gastrointestinal complications, which were the most common diagnoses at admission in both groups, but were still more common in patients with PD. Also, these were the most common reasons for admission among the older age group with PD compared to those in the same age group without PD. These are in line with my systematic review where I found infections, falls/fractures and gastrointestinal complications as top reasons for admission among people with PD in the nine included eligible studies. The percentages of these reasons for hospitalisation were lower than the meta-analysis estimates. This could be due to my use of incident PD cases followed up for ten years after diagnosis. The percentages might have been higher if I included prevalent cases like the eligible studies included in the review. Nonetheless, People with PD were still being admitted for infections, falls/fractures and gastrointestinal complications than people without PD even though only two (Lubomski M et al., 2014, Braga

M et al., 2014) of the nine eligible studies included a comparator group (**see Chapter 2 and Appendix 2-1**).

In addition, patients with PD were more often admitted due to their PD itself, postural hypotension, electrolyte disturbances, surgical procedures, dementia and particularly psychosis/hallucinations, which were seven times more common in the PD population. This is in keeping with the known features of advancing PD, including its increasing motor complications with freezing, motor fluctuations and postural instability, and a range of non-motor symptoms such as neuropsychiatric complications, postural hypotension, constipation, urinary dysfunction and complications of treatment, including electrolyte disturbances, dyskinesias and hallucinations (Schrag A et al., 2002, Jankovic J, 2005). Deteriorating motor control may lead to admissions either due to deterioration of mobility or the consequences of falls and fractures (Schrag A et al., 2015), dysphagia leading to aspiration pneumonia (Schmidt J et al., 1994, Gross RD et al., 2008, Suttrup I and Warnecke T, 2016), bladder dysfunction leading to urinary tract infections, constipation necessitating admission, and antiparkinsonian medication together with PD contributing to postural hypotension (Lubomski M et al., 2014, Braga M et al., 2014) and electrolyte disturbances, and exacerbating delusions particularly in those with dementia. Whilst some of these are not necessarily preventable, careful monitoring for infections, falls risk assessments, assessment of bladder residual and rapid testing for urinary tract infections, adjustment and review of medication, and swallowing assessments and multi-disciplinary treatment such as speech therapy and physiotherapy (Keus SH et al., 2012), all have the potential to

reduce the risk of hospital admission (Baijens LW and Speyer R, 2009, Kalf JG et al., 2012).

Of note hypertension was slightly less common reason for admission in those with PD than those without PD, which may be a reflection of the reduction of blood pressure by PD and antiparkinsonian medications. Similarly, in the older age group, myocardial infarction/ischaemic heart disease and congestive heart failure was a less common diagnosis at admission in the PD cohort. On the other hand, stroke was a more common reason for admission in people with PD in the older age group, even after adjustment for smoking. This has not been previously reported but it could be speculated that blood pressure variability with hypoperfusion and nocturnal supine hypertension may increase the risk of stroke (Berganzo K et al., 2013). This finding highlights the importance of carefully managing complication of postural hypotension, which often significantly affects quality of life but is typically difficult to manage and may result in supine hypertension. On the other hand, cancer in the younger age group, myocardial infarction/ischaemic heart disease and congestive heart failure, were not different between patients with PD and matched controls and in older age group, myocardial infarction/ischaemic heart disease and congestive heart failure were less common, perhaps reflective of the lower rate of hypertension.

Similar to this study, several studies (Tan L et al., 1998, Pressley JC et al., 2003, Guttman M et al., 2004, Paul BS et al., 2017) including my systematic review (**see Chapter 2 and Appendix 2-1)** have reported infections, falls and fractures as the main reasons for hospital admissions among people with PD.

Falls are reported to be more common in people with PD than people without PD (Wood BH et al., 2002, Amar K et al., 2015, Owen CL et al., 2019). Incidence of falls and fractures was reported to increase with increasing age in both PD and general population in previous studies (Kalilani L et al., 2016). In addition, the risk of falls and fractures was reported to double after 65 years of age in the general population whilst in the PD population, the risk steadily increased from 40 years indicating that factors inherent to PD such as severity of disease and functional disability may be key determinants of the risk of falls and fractures in these patients (Huang YF et al., 2015, Kalilani L et al., 2016).

Psychosis/hallucinations were considerably more common in the PD cohort than in the non-PD cohort, and this difference was most marked in the younger age group, with a 19-fold increase in risk of admission compared to non-PD cohort. Dementia was also a more common cause of admission in the younger age group, with a 11-fold higher rate compared to controls and is known to be associated with psychosis in PD. Whilst we did not examine medication doses, antiparkinsonian medication doses are typically higher in the younger age group which is likely to have contributed to the higher rate of hallucinations and psychosis (Friedman JH, 2013, Ffytche DH et al., 2017, Simonet C et al., 2020) as well as to the higher rate of postural hypotension as a more common cause of admission in the younger age group of patients with PD.

Previous reports on the rates of admission for cardiovascular diseases and stroke in the patients with and without PD have provided mixed results (Pressley JC et al., 2003, Lubomski M et al., 2014, Braga M et al., 2014). Some studies (Pressley JC et al., 2003) showed that people with PD compared to

those without PD are more likely to be admitted for cardiovascular diseases such as myocardial infarction/ischaemic heart disease, chronic heart failure and stroke while others found no difference or less representation (Vossius C et al., 2010, Braga M et al., 2014, Lubomski M et al., 2014). Overall, there is speculation that the risk of cardiovascular diseases and stroke is low in people with PD. This is attributed to reduced vascular risk factors and lower smoking rates in people with PD. However on the contrary, in a recent meta-analysis, the risk of cardiovascular disease and stroke were reported to be higher in PD especially in the older age group (Hong CT et al., 2018), similar to this study.

In keeping with previous studies (Lubomski M et al., 2014), reason for admission attributed to cancer was not different between those in the PD cohort and non-PD cohort. This was same for both PD age groups. The risk of cancer has previously been reported to be lower in PD compared to control populations (Bajaj A et al., 2010, Becker C et al., 2010).

In this study, we show that people with PD were more likely to be admitted for gastrointestinal complications including dysphagia, nausea and vomiting and constipation compared to the control cohort with higher rates in those 70 years and more possibly due to advanced disease. There are few studies which have reported gastrointestinal complications as a reason for hospital admissions among people with PD. Similar to my study, one study (Lubomski M et al., 2014) reported gastrointestinal complications as a top reason for hospitalisation in PD. Gastrointestinal problems such as dysphagia may lead to swallowing problems resulting in aspiration pneumonia which is reported to be the commonest cause of death in people with PD (Iwasaki S et al., 1990, Beyer M et al., 2001,

Pennington S et al., 2010). Early identification of dysphagia through regular assessment of swallowing function and implementation of changes to dietary consistency may prevent aspiration pneumonia (Guttman M et al., 2004) and subsequent hospitalisation.

6.10 Strengths and limitations

This is the first study to our knowledge to investigate incidence rate of hospitalisation among people with PD in the UK using prospectively collected data from a large primary care database which is generalisable to the UK population. In addition to my large cohort size, a strength of this study is that I examined incident cases which allow follow-up from early disease and is more informative on an individual prognostic basis. This study also highlights important reasons (gastrointestinal complications and postural hypotension) for hospital admission in PD. I also used a frequency-matched cohort which would help prevent potential confounding of the rate ratios. The only downside of this is that the effects of some factors (for example gender) on study outcome may not be observed as in my study. However, the study has generated baseline data which can be used for planning of healthcare services for these patients and support initiatives to reduce hospital admissions in PD.

The main limitation of this study is that I was unable to validate hospital admissions/hospitalisations or reasons for hospitalisation in the database since these data were based on primary care recording of secondary care reports, which may have led to underreporting of admissions and diagnoses. There is no reason to believe this underreporting would be different in those with PD and those without PD. This may have however led to a non-differential

misclassification bias, which might underestimate the true difference in admission rates between those with PD and without PD. There is also the possibility of misclassification which could result from using Read codes as surrogate measure for hospitalisation as some of the codes may not be related to an event of hospital admission.

Attribution of symptom recording in relation to admission may also not be precise as coinciding admission date and symptom recording does not necessarily indicate they are directly related. As causes of hospitalisations were identified by using diagnoses entered within a time frame of 28 days of admission, and as it was based on primary care records only, the results need to be interpreted with caution. Also, for some admissions, the diagnosis associated with admission could not be determined.

Another limitation is that I was unable to account for the presence/absence of caregivers which may contribute or modify risk for hospital admissions, and disease severity because this is not well recorded in this database. Nevertheless, this is by far the largest study of hospital admissions and PD conducted to date, in a representative sample and based on routine records, avoiding recall and selection bias. These data therefore provide reasonably robust information on the rate and diagnoses associated with admissions of patients with PD.

6.11 Summary of the chapter

In this chapter, I have presented the results of an exploratory study investigating hospital admissions among patients with PD and show that rates of hospital admissions among people with PD in the UK are higher than matched controls without PD. People in the youngest age group had rates

which were almost double that of their counterparts without PD. Gastrointestinal complications in addition to previously known factors such as infection, falls and fractures seem to contribute to an increased rate of hospital admissions in these patients. This is the first and largest study to investigate hospitalisation in UK and results are comparable to results from USA and Canada. In Chapter 7, I will highlight the key findings of all studies in this thesis and discuss these findings in the context of published literature. I will also describe the implications of my findings on clinical practice and public health policy and discuss directions for future research.

Chapter 7 Discussion, Implications and Conclusion

7.1 Chapter overview

In this final chapter, I present a summary of the key findings from all four studies included in this thesis and also discuss these findings in the context of existing literature. Then I present the implications of my findings for clinical and public health practice and policy and I provide suggestions for potential directions for future research and lastly, I present a conclusion.

7.2 Summary of main objectives of this thesis

The main objectives of this thesis were associated with outcomes of disease progression in Parkinson's disease (PD). These are summarised below

1. To summarise previous literature on hospitalisation and synthesize pooled estimates of prevalence of the common causes of hospitalisation among people with PD through systematic review and meta-analysis **(Study 1-Chapter 2).**
2. To estimate changes in incidence of PD between 2006 and 2016 in The Health Improvement Network (THIN) and its association with age, gender, social deprivation and regional location of practice using four different case definitions generated from combination of diagnosis Read codes, symptom Read codes and treatment codes **(Study 2-Chapter 4).**
3. To explore mortality in people with PD compared to frequency-matched individuals without PD in the UK and its association with disease duration, age, gender and social deprivation **(Study 3-Chapter 5).**

4. To estimate the rate of hospital admissions in the UK among people with PD and to explore factors associated with hospitalisation in people with PD compared to those without PD **(Study 4-Chapter 6).**

7.3 Key findings of my research

A summary of each study and the main findings are described below:

Study 1. Factors associated with hospitalisation among people with Parkinson's disease: A Systematic Review and Meta-analysis.

My systematic search of the literature identified nine eligible studies which were relevant for inclusion in the review **(see Chapter 2).** There was high heterogeneity among these studies due to varied reasons for hospitalisation identified. Most of the included studies were retrospective and I hypothesized that some reasons for hospital admissions may be underrepresented due to possibility of recall bias. However, the main reasons for hospitalisation identified included infections, worsening motor features of PD, falls/fractures, cardiovascular comorbidities and neuropsychiatric complications.

Study 2. Incidence of Parkinson's disease in The Health Improvement Network

In Chapter 4, I estimated the incidence of PD recording in THIN between 2006 and 2016 using four case definitions: [1] definition based on PD diagnosis Read codes and at least two prescriptions of antiparkinsonian medication (strictest and most specific case definition). This strictest definition was then also used to identify incident cases for the cohort studies presented in this thesis (Chapters 5 and 6); [2] definition based on only diagnosis Read codes; [3] definition based

on diagnosis Read codes OR symptom Read codes; [4] definition based on diagnosis Read codes OR symptom Read codes OR at least one prescription of antiparkinsonian medication (broadest and most sensitive case definition). There was a decreasing trend in the number of recordings of PD diagnosis over time using the stricter case definitions similar to previous similar study (Horsfall L et al., 2013), but a broadly stable trend using the most sensitive case definition. Similar to the previous study in THIN (Horsfall L et al., 2013), using all case definitions, findings from my study showed that men, those age 80 to 84 years and those living in the least deprived areas had higher rates of PD diagnoses recorded. On the other hand, using the stricter case definitions, overall rates of incidence of PD were lower than rates from the previous study (Horsfall L et al., 2013). However, overall rates from my study was similar to the study by Parkinson's UK using a different but comparable dataset (Parkinson's UK: Reference Report, 2017). They reported an overall incidence rate of 71 per 100,000 in individuals aged 50 to 94 years between 2011 and 2015 using only the diagnosis Read codes for PD, which is similar to my incidence rate of 70 per 100,000 using these diagnosis codes in this age group.

Validation of these case definitions would be valuable to ascertainment of PD diagnosis in THIN and other primary care databases for future research. In addition, those living in Northern Ireland had higher rates of PD recordings using all case definitions. This could be due to differences in healthcare systems.

Study 3. Mortality in Parkinson's disease-a large UK-based cohort study, Time trends and relationship with disease duration.

In Chapter 5, using the strictest case definition, I identified 10,104 incident cases of PD (PD cohort). These were matched within practice for age, gender and calendar year with 55,664 people without PD (non-PD cohort). I investigated trends in mortality and factors associated with mortality in the people with PD compared to people without PD.

Overall, PD was associated with slightly increased mortality compared to non-PD cohort by 14% (adjusted mortality rate ratio: 1.14 (95% CI 1.03 to 1.19). Adjusted mortality rates progressively increased with each year following diagnosis of PD and almost doubled by five years after diagnosis from 43 (95%CI: 38 to 48) to 75 (95%CI: 64 to 85). Between 2007 and 2016, there was a declining trend in mortality of about 2% per year in the PD cohort whereas it decreased by 5% per year in the non-PD cohort after adjustment for age, gender, time since diagnosis, smoking and social deprivation, resulting in an increasing mortality rate ratio (mortality gap in those with PD compared to those without PD) over the observation period. Sociodemographic factors did not influence the differences in mortality rates between PD and non-PD cohorts. These data highlight the impact of advancing disease on mortality and suggests that the mortality gap between people with and without PD is either due to comorbidities associated with PD or characteristic features of PD itself.

Study 4. Rate of hospitalisation and underlying reasons for hospitalisation among people with Parkinson's disease in UK primary care-An exploratory cohort study.

In Chapter 6, I investigated the incidence rate of hospitalisation among people with PD in the UK using the same study participants from Chapter 5 after excluding a small number with missing/retrospective recording of hospitalisation event date. I also investigated reasons for hospitalisation among people with PD compared to people without PD.

People with PD were 1.33 times more likely to be hospitalised compared to those without PD after adjustment for age, gender, calendar year, social deprivation, urbanicity and geographic location of practice. Also, adjusted rates of hospitalisation rose from the year after PD diagnosis and increased with increasing disease duration. Overall, hospitalisations were higher in the older age groups, but the adjusted incidence rate ratio of hospitalisation in people with PD compared to those without PD was highest in the youngest age group (IRR 1.79, 95%CI: 1.52 to 2.11).

People with PD were more often admitted with falls, fractures, infections (mainly chest, urinary tract and skin and subcutaneous tissue infections), gastrointestinal complications (dysphagia, constipation nausea and vomiting), dementia, psychosis/hallucinations, postural hypotension, electrolyte disturbances, stroke, surgical procedures compared to those without PD. Conversely those with PD were slightly less often admitted for hypertension compared to those without PD. There were no differences in the rates of admissions for myocardial infarction, chronic heart failure and cancer between

people with PD and those without PD. As causes of hospitalisations were identified by using diagnoses entered within a time frame of 28 days of admission, and as it was based on primary care records only, the results need to be interpreted with caution. However, no comparable studies on incidence and causes of hospitalisations in PD exist in the UK and my results are comparable to those of previous studies from USA and Canada.

7.4 Discussion

The main objectives of this research are related to outcomes and prognosis of PD which include hospital admissions and mortality. However, I will discuss the results of Incidence of PD first as the study population for the other studies in THIN were derived through this study. In the second part of the discussion, I will focus on hospitalisation in PD. In the third part I will focus on mortality in PD.

7.4.1 Incidence of Parkinson's disease in UK primary care

I show that case ascertainment is very important in research using large databases as different definitions yielded different results. Using the stricter case definitions, there was a gradual decline in the incidence of PD diagnosis recording in primary care between 2006 and 2016. This is in keeping with a previous similar study (Horsfall L et al., 2013) conducted by three of my supervisors during a different time frame (1999 to 2006). However, changing diagnostic guidelines **(see Chapter 1)** could have affected diagnostic coding. Using the broadest and most sensitive case definition, the incidence was stable **(see Chapter 4).** Using the broadest and most sensitive case definition allows for comparison with previous studies and showed an overall increase in

incidence but stable trend in incidence of PD over time. This case definition may however be too inclusive with possibility of too many false positives.

The strictest definition used at least two prescriptions in addition to PD diagnosis code to increase the specificity of this case definition. Analysis using the strictest case definition alone however may not capture all patients with PD and carries a risk of wrongly concluding a decline in incidence based on the strictest case definition. In addition, comparison with previous studies which used different definitions is difficult. I therefore present results from four case definitions. However, for the following studies examining PD outcomes, I used the strictest case definition in order to avoid false associations, since it is the most specific and therefore robust (fewer false positive cases) and has been shown to have a validity of 90% in GPRD. This case definition is however the least inclusive with the possibility of too many false negatives but robust.
Validation studies using these case definitions would be key for future research. Knowing the trends in incidence over time and by socio-demographic characteristics may be helpful for service planning for example projecting future need for specialist PD services.

7.4.2 Hospitalisation in Parkinson's disease

With progressive disease, the severity of PD worsens over time leading to increased risk of hospitalisation. I showed that people with PD were 1.33 times more likely to be hospitalised compared to the general population in the UK **(see Chapter 6).** Whilst there are no UK studies, this rate is comparable to studies from USA (Pressley JC et al., 2003) and Canada (Guttman M et al., 2004) with different healthcare systems, albeit at the lower end on the spectrum.

People with PD in the younger age group had higher rates of admission compared to those in the younger age group without PD, mainly reflecting the increased rate of admissions also in the control population with advancing age, but also suggesting the possibility of increased rate of complications in the younger age group (for example infections, falls and gastrointestinal complications) relative to others of the same age without PD. Other sociodemographic variables did not influence the differences in the rates of hospitalisation between people with and without PD.

Data from this study can be used to develop policies and clinical trials targeted at preventative strategies which would address the identified potential reasons for hospitalisation. My findings showed that people with PD have an increased risk of admission for a wide range of causes, many of which may be modifiable with pro-active/earlier intervention. For example: for falls/fractures prevention, a network of physiotherapists who are specially trained in PD and based in the community organising exercises regularly for patients with PD could lead to improvement in their mobility with potential reduction in rate of falls leading to reduction in hospital admissions (Munneke M et al., 2010). For prevention of infections, regular inquiring about urinary symptoms and disorders and careful monitoring of the general condition of patients with PD could lead to early diagnosis and treatment of infections (urinary and other infections) that lead to hospital admissions. Also, early recognition and treatment of constipation could reduce urinary retention and infection. Furthermore, regular swallowing assessments with changes in dietary consistency may help prevent aspiration and respiratory tract infections (Koay L et al., 2018) leading to a reduction in hospitalisations and sometimes mortality resulting from these infections. The

focus of future research should be to determine the clinical and cost effectiveness of these different preventive strategies in order to reduce hospital admissions among people with PD.

7.4.3 Mortality in people with Parkinson's disease

The overall mortality rate in people with PD was higher than those without PD (unadjusted mortality rates per 1000 person-years: PD cohort 56.06 vs non-PD cohort 50.07). In addition, mortality rates declined in both groups over the study period but at a faster rate in those without PD resulting in a mortality gap between both groups which was largely driven by increasing mortality in people with PD with longer disease duration.

It has previously been suggested that some interventions addressing morbidity and disability may have had an impact on survival in people with PD. There have been speculations that the introduction of levodopa might have contributed to this reduction in mortality, but there is no robust evidence (Macleod AD et al., 2014). The finding of this study however suggests that the symptomatic treatments available for PD during the study period have not eliminated the increased mortality associated with PD and in fact people with PD have not seen the same reduction in mortality as those without PD. It is unclear whether certain comorbidities or PD itself are responsible for these differences in mortality rates. Although, I adjusted for smoking, recent reports showed that smoking has been declining in the general population and is thought to be a key cause for reduced mortality and we know people with PD smoke less, so are less likely to gain from this. This would require further investigation. Also, findings from my study showed that mortality gap is

widening, and more research is needed to understand why this is, and interventions to address this gap.

7.4.4 Potential causes of the increased mortality in Parkinson's disease

There are a range of potential causes for the observed increased mortality in PD in my thesis.

7.4.4.1 Complications of Parkinson's disease and of antiparkinsonian medications.

Side effects of antiparkinsonian medications include motor fluctuations and dyskinesias; hallucinations, nausea and vomiting, orthostatic hypotension; cognitive or autonomic symptoms (Singer C, 2002); pulmonary and retroperitoneal fibrosis, vasoconstrictive effects (rare, caused by ergot-derived dopamine agonists) (Lambert D and Waters CH, 2000). Some of these complications are very serious and could be life-threatening. For example, dyskinesias (involuntary movements) when severe can cause falls leading to fractures or head injuries and may be death in some instances (Simonet C et al., 2020). Some patients may develop Parkinsonism-hyperpyrexia syndrome following a sudden change in dopaminergic medication. An acute akinetic attack is a serious complication with an incidence of 0.3% and mortality of 4% (Onofrj M and Thomas A, 2005, Newman EJ et al., 2009, Onofrj M et al., 2009). It is characterised by significant global slowness, generalised muscle rigidity and hyperthermia. As the akinesia worsens, systemic complications such as aspiration pneumonia due to rigidity and reduced level of consciousness; acute renal failure due to rhabdomyolysis and dehydration (Simonet C et al., 2020) lead to hospitalisation and may be death. Another complication which occurs

with long-term dopaminergic treatment is acute psychosis. It is reported to occur in 30% of such patients and associated with poor prognosis and high mortality (Friedman JH, 2013). A well-established inherent aspect of PD are psychotic symptoms such as hallucinations. These symptoms are frequently triggered and provoked by antiparkinsonian medications and are reported to be predictors of imminent cognitive decline (Ffytche DH et al., 2017). Regular changes in antiparkinsonian medications, some antidepressants and painkillers can trigger or worsen psychotic symptoms in PD. In addition, infections, surgical procedures, toxic-metabolic disturbances and neurological disorders (for example subdural haematoma from falls) can also provoke or worsen psychotic symptoms (Simonet C et al., 2020) resulting in worsening outcomes.

7.4.4.2 Hospital admissions and re-admissions

Hospitalisation of people with PD has been reported in studies in around 7% to 28% of patients with PD yearly (Gerlach OH et al., 2011). Whilst admitted, patients with PD can suffer a worsening of their motor symptoms, treatment related complications and complications such as falls, infections (aspiration), poor control of the disease, prolonged immobility and pressure sores which may lead to death particularly after surgical procedures (Pepper PV and Goldstein MK, 1999, Mueller MC et al., 2009, Aminoff MJ et al., 2011, Gerlach OH et al., 2011). In addition to longer hospital stay, morbidity and mortality are reported to be higher than controls (Aminoff MJ et al., 2011, Gerlach OH et al., 2011).

7.4.4.3 Comorbidities in Parkinson's disease

Several comorbidities have been reported to be increased in people with PD compared to the general population. These include depression, anxiety, dementia and hypertension which are associated with worse outcomes (Marsh L et al., 2004, Aarsland D et al., 2005, Reijnders JSAM et al., 2008, Pohar SL and Allyson Jones C, 2009, Gil-Prieto R et al., 2016). Although not well established due to heterogeneity in selection of study population, methodology and results (Macleod AD et al., 2014), comorbidities such as dementia and depression are linked to disease severity and mortality in PD (Riedel O et al., 2014).

7.4.4.4 Features of advanced Parkinson's disease

In spite of treatment with antiparkinsonian drugs, some features of PD remain troublesome, worsen and may lead to increased hospital admissions and mortality (Nussbaum M et al., 1998). Features such as falls occur in 50% to 60% of patients as the disease progresses (Michałowska M et al., 2005). Falls result from impairment in postural reflexes, gait freezing, severe dyskinesias and orthostatic hypotension (Schrag A et al., 2015). These result in fractures, reduced mobility and functional regression and subsequent increased risk of mortality (Michałowska M et al., 2005).

Dysphagia is another burdensome feature of PD which commonly occurs in advanced disease (Factor SA and Molho ES, 2000). It results from oropharyngeal bradykinesia and loss of coordination in the normal process of swallowing resulting in frequent coughing, choking, regurgitation during meals and frequent respiratory infections. Dysphagia is a feature of PD which is

associated with increased rate of mortality because of aspiration pneumonia which is reported to be the commonest cause of death in these patients (Pennington S et al., 2010, Poirier AA et al., 2016). Being a progressive neurodegenerative disease with increasing multiple treatment-resistant features especially in advanced disease, it is more likely that PD “itself” leads to increased mortality.

7.4.4.5 Reduced healthcare access compared to the general population

Difficulties in appropriate engagement with the healthcare system and failures of healthcare system itself can result in poor healthcare access. Patients may have difficulty attending healthcare services if they are older and frail or have severe disability from the disease. Others may actively avoid contact with services from the healthcare system due to poor adherence to treatment generally. Due to cognitive deficits or symptoms, some patients may have difficulty interpreting and communicating their health problems and needs. In addition, tasks such as making appointments, comprehending healthcare or carrying out instructions given may be difficult to undertake without additional support which may not be available.

Some of the specific troublesome features of PD may not be easily recognised by non-neurologists and could be missed resulting in hospital admission and potential mortality. It has been reported that less than half of PD patients get treated by neurologists (Willis AW et al., 2011) suggesting that others receive care from other physicians in the community who may not have the appropriate expertise to manage the troublesome symptoms of the disease.

7.4.5 What can be done to address increased mortality?

There are a number of preventative strategies which may help address the increased mortality in people with PD. These include:

7.4.5.1 Reducing medication related problems

There are currently no treatments to halt the progression of PD. However available medications provide symptom control but sometimes cause worsening of motor features particularly in advanced disease. In order to prevent some medication related complications, treatment should be aimed at providing a constant dopaminergic drug supply to the brain (Salat D and Tolosa E, 2013). Gradual levodopa dosing through the day (avoiding abrupt changes) and adjustment of other adjunctive antiparkinsonian medications can reduce fluctuations and dyskinesias (Melamed E et al., 2007). These may reduce hospitalisations and mortality in PD.

There are reports that adherence to antiparkinsonian medications could be linked to reduction in hospital admissions due to worsening motor symptoms of PD (Kulkarni AS et al., 2008, Davis KL et al., 2010, Delea TE et al., 2011, Wei YJ et al., 2014). Motor outcomes, other complications of the disease and quality of life of patients with PD can be negatively impacted by sub-optimal adherence to antiparkinsonian medications. These imply that optimising symptom control in patients with PD through compliance with antiparkinsonian medication may lead to a reduction in hospitalisations due to poor motor control particularly in countries where some patients lack health insurance thereby making interventions such as frequent neurologist/other clinician care and open access clinics difficult (Grosset D et al., 2009, Klein C et al., 2009).

It is also important to ensure antiparkinsonian medications are affordable and readily accessible by all patients with PD. Furthermore, a list of medications that could worsen symptoms of PD should be made available to patients and their care givers.

Adverse effects of antiparkinsonian medications should be communicated to patients before starting them on the medications. For example, patients who are prescribed dopamine agonists should be informed about side effects such as impulse-control disorders and sleep attacks prior to taking the medication and while on the medication. Also, where a patient requires elective admission, prior planning of medication changes should be a key part of the process. For example, where oral medication intake is limited, this should be substituted for transdermal agonists, enteral administration of usual medication, and levodopa-carbidopa intestinal gel infusion (Simonet C et al., 2020).

7.4.5.2 Preventing complications of Parkinson's disease

Complications such as falls, fractures, infections, dysphagia, cognitive and motor symptom deterioration are recognised risk factors for hospitalisations (Hassan A et al., 2013) and may result in death of patients with PD. Hospitalisation and mortality may be reduced by executing preventative measures for these complications. Falls could be prevented by improving motor symptom control and managing side effects of antiparkinsonian medications. Additionally, motor features, mobility and balance which predispose patients to

falls are thought to improve with physiotherapy and may reduce risk of falls (Muzerengi S et al., 2016). With regards to prevention of fractures, measures such as Vitamin D supplementation and bisphosphonates may improve bone mineral density thereby preventing osteoporosis and reducing the risk of fractures. In a previous study, the effect of treatment or no treatment with fracture prevention medication on mortality was compared in an Italian study of 5167 postmenopausal women. When fracture treatment was used, incidence of death and re-fracture related hospital admissions were reported to have significantly reduced (Tarantino U et al., 2011)

Rehabilitative therapy if started early may prevent dysphagia and related complications. Dysphagia management including speech and language therapy may reduce hospitalisations due to aspiration pneumonia which is common sequelae of dysphagia. This may also lead to a reduction in mortality in patients with PD since aspiration pneumonia is a well-recognised cause of death in these patients (Muzerengi S et al., 2016, Simonet C et al., 2020). There are no available studies which have systematically assessed these preventative measures on hospitalisation and mortality in PD.

7.4.5.3 Improved healthcare access

- **Improved access to neurological/general care/services**

  Open access clinics, frequent consultations by neurologists, training generalists and medication compliance by PD patients may lead to reduction in hospitalisations and mortality in these patients (Muzerengi S et al., 2016). Patients with PD when hospitalised suffer worse outcomes

including worsening of their symptoms, medication error and infections which may lead to death (Muzerengi S et al., 2016). Therefore, Open access clinics may provide opportunities for Neurologists/Clinicians to manage symptoms and other complications of the disease which may prevent unwanted hospitalisations and in some instances death. The effectiveness of open access clinics was reported in a study from a single centre which did not include comparison group. The authors adopted an "open door" policy where they allowed some patients with PD attend clinic without prior appointment if they or their caregiver thought there was an urgent need. Patients who were prescribed a new medication or change of regimen were invited for a follow-up within a month (Klein C et al., 2009). Others suffering severe hallucinations, delusions, sudden onset prolonged "offs" and orthostatic problems were allowed to immediately attend the clinic where they received immediate treatment and were monitored for some hours before being discharged. The authors reported that number of hospital admissions and critical situations decreased (Klein C et al., 2009).

Similarly, improvement of community-based PD care and regular neurological consultations may provide opportunities for early interventions such as adjustment of medications, detection and management of comorbidities and complications resulting in prevention of hospitalisation and maybe death (Klein C et al., 2009, Willis AW et al., 2012).

Education of general practitioners and other clinicians about care of PD patients particularly with regards to drug use in PD could reduce hospitalisations and maybe mortality in PD. Of note is the use of some

antiemetics for example metoclopramide which worsens symptoms of PD and should be avoided. Additionally, such training could include identification of atypical features of urinary tract infections including worsening motor symptoms of PD, confusion or psychosis which may be mistakenly diagnosed as progression of the disease (Esper CD and Factor SA, 2008, Hufschmidt A et al., 2010). Educating PD patients to optimise self-management and empower them to better manage their own condition could also help in reducing complications that lead to hospitalisation and maybe death.

- **Access to Parkinson's disease community care**

Patients with PD in the community who are at high risk of hospitalisation and mortality may be identified by PD specialist nurses where they are available. Early treatment can therefore be instituted in patients' homes by the PD nurse together with other PD specialists in primary and secondary care, social services, palliative care and rehabilitative therapy (Muzerengi S et al., 2016). Additionally, PD nurse specialist can be supportive of patients and their caregivers. They can clarify patient concerns and help with implementing a treatment plan (Simonet C et al., 2020). These may lead to a reduction in unplanned hospital admissions and maybe mortality in PD.

7.5 Implications of findings from studies on mortality in Parkinson's disease

In this section I list some of the key points for patients, clinicians, policy makers and research from each of my studies.

7.5.1 Important points for patients and clinicians

a) Overall, mortality is higher in people with PD relative to the general population.
b) Mortality rates are slowly decreasing in people with PD.
c) Mortality rates in the general population is decreasing at a faster rate thus out pacing rates in people with PD resulting in an increasing mortality gap.
d) Advancing disease appears to be the main driver of mortality in people with PD and measures to slow disease progression or more effectively prevent associated complications should be sought.

7.5.2 Important points for policy makers

a) Current interventions and policies in place for the general population seem not to impact mortality rates in people with PD and thus not addressing mortality gap in these group of people.
b) Since my study has showed mortality gap between people with PD and those without PD was increasing to 2016 and perhaps beyond, it is therefore important to track long term mortality (through electronic medical records and use of updated software systems) and see if inequality is widening or narrowing to service changes or interventions.
c) The apparent increase in mortality rates in PD relative to the general population after the end of this study period (2016) should be explored to see if this is a continuing trend so that interventions can be developed reduce mortality among these patients.

d) Surveys/audits on implementation of available guidelines/services with regards to PD care should be conducted yearly in order to identify and provide interventions where there are gaps which may lead to reduction in mortality for example medication management, access to available services such as PD nurse and other PD specialist services (occupational therapy & physiotherapy for prevention of falls), patient with swallowing problems engagement with Speech and Language Therapy (SALT). Evaluating and monitoring the use of these services may identify areas for improvement, with a view to implementing changes and address the widening mortality gap.

e) Pro-active care/interventions to prevent complications and admissions across healthcare settings should be made available. This could be through support for people with PD and their carers to self-manage and support for frontline non-specialists (for example GPs and emergency doctors).

f) Annual reviews for complications such as falls/fractures, swallowing problems, autonomic and psychiatric complications could be incorporated in general care of PD.

7.5.3 Important points for researchers

a) More research is needed to understand the reasons for the relative mortality increase in people with PD compared to the general population. Following this, further research will be needed to test interventions to address the reasons for the widening mortality gap, if applicable.

b) There is need for researchers to better identify specific predictors of mortality in PD particularly modifiable factors such as comorbidities (for

example cardiovascular diseases, stroke, diabetes etc) and other treatable characteristic features of PD (for example falls, postural hypotension etc).

c) Further research should test the clinical and cost effectiveness of interventions to reduce mortality in people with PD.

7.6 Implications of findings from studies on hospitalisation in Parkinson's disease

7.6.1 Important points for patients and clinicians

a) Rates of hospitalisation is higher in people with PD than the general population resulting in increased morbidity.

b) Overall, rates of hospitalisation are higher in older patients with PD.

c) Notably, rates of hospital admissions are relatively higher in the younger PD patients than people without PD in the same age group.

d) People with PD are more often admitted for gastrointestinal complications, psychosis/hallucinations, postural hypotension and varying surgical procedures in addition to well-established reasons for admission such as falls/fractures and infections.

7.6.2 Important points for policy makers

a) There are increased rates of hospital admissions among people with PD.

b) Some causes of admission such as dysphagia resulting in pneumonia, falls/ fractures and infections are well-established causes of death in PD.

c) Policies to improve community care may reduce hospitalisation and mortality in PD.

d) Surveys/audits to identify potentially modifiable causes of admissions in PD and implementing changes to address these causes should be encouraged. These surveys can be done pre and post implementation of the intervention/service.

e) Funding for research of interventions/services which could reduce hospitalisation and potentially mortality should be encouraged.

7.6.3 Important points for researchers

a) The search for disease modifying treatment is admirable but research on how to prevent hospital admissions in people with PD and reduce mortality should be encouraged.

b) Research on interventions (for example targeted at prevention of falls, pneumonia and fractures) aimed at reducing hospitalisations in people with PD is lacking. More clinical trials on the clinical and cost-effectiveness of interventions aimed at reducing hospital admissions are needed.

c) Evidence on whether more frequent consultations, specialists' clinics and medication management may reduce hospital admissions in PD is limited requiring further research.

d) Development and testing of interventions to support the self-management of PD patients that addresses potentially modifiable causes of admission.

7.7 Future research directions

7.7.1 Including secondary care data

Findings from my research were restricted to primary care setting given that the data source for my research was primary care electronic medical records that had not been linked to secondary care data. Ideally, future studies should investigate presentations of PD patients to both primary and secondary care services since patients seek healthcare from both settings. This could be done by linking data from a primary care data source such as THIN to data from Hospital Episode Statistics (HES) in instances where individuals have electronic records in both databases. This could particularly provide a more precise overview of hospital admissions and additional data on mortality as data from secondary care would be captured.

Additionally, missingness of data on some variables for example ethnicity and social deprivation may be reduced. There are reports of completeness of up to 97% of data on ethnicity in those with electronic records in both HES and primary care database (Mathur R et al., 2014). Such data completeness could have allowed me the opportunity to investigate the relationship between ethnicity and mortality and hospitalisation in people with PD. Also, while investigating the effects of sociodemographic factors on mortality and hospitalisation in PD, ethnicity as a potential confounder could have been accounted for.

Other advantages using HES linked data include: identification of additional PD cases registered with a practice not captured by the case definition (algorithm)

described in chapter 5; the availability of additional data on time of diagnosis (Millett ERC et al., 2016), reasons for hospitalisation and cause of death in these patients. One drawback of the HES linkage data is decrease in sample size. For example, only twenty-three percent of the practices contributing data to THIN have been linked with HES. Other primary care databases such as CPRD GOLD and CPRD AURUM with about 56% and 43% of practices respectively linked to HES data (Padmanabhan S et al., 2018, IQVIA, 2021) were not available to me.

7.7.2 Identifying predictors of mortality in people with Parkinson's disease.

Knowledge on factors that influence mortality among people with PD is very important given the slow progressive nature and increased mortality with longer duration of the disease as I have shown in Chapter 5. Cognitive impairment/dementia, old age, late age of onset, male gender and gait abnormalities have been reported to increase mortality risk among people with PD (Bennett DA et al., 1996, Beyer M et al., 2001, Hughes TA et al., 2004, Duarte J et al., 2013). Most of these factors are non-modifiable and well-established predictors of mortality in PD. There are however some comorbidities which are modifiable and may be important factors linked with increased mortality in people with PD which are yet to be explored. There is currently little information on these key modifiable predictors of mortality. In a recent systematic review, excess mortality in people with PD was reported to be a result of comorbidities, complications associated with PD itself and the authors suggested that comorbidities as predictors of mortality in PD should be investigated (Xu J et al., 2014). The term comorbidity is used to designate the

co-occurrence of two or more clinical disorders which may or may not share similar pathogenesis (Shulman LM et al., 2001). Some comorbidities such as hypertension, ischaemic heart disease/myocardial infarction, diabetes mellitus, anxiety, depression, epilepsy, headache may be important modifiable factors which may be associated with increased mortality in PD. Investigating the impact of these comorbidities on mortality is key to planning interventions in the trajectory of the disease. Since most of these comorbidities are recorded in THIN, they could be easily investigated using the database. Early identification and prompt treatment of these comorbidities can help reduce mortality in PD resulting in improvement in the prognosis and survival of patients (Xu J et al., 2014).

7.7.3 Validation of hospital admission in primary care data

In the past two decades, digitisation of health records in the UK and other parts of the world has become widespread and resulted in an exponential growth in the use of routinely collected healthcare data for research (Casey JA et al., 2016). This has led to increasing use of primary care databases (for example THIN: Chapter 3); a source of data for epidemiological research. Establishing the accuracy of diagnoses recorded by General Practitioners is an important preliminary step in using automated health care databases for epidemiological research (Martín-Merino E et al., 2012). This could be used to assess/measure the burden of hospital admissions in UK population registered with a practice contributing data to THIN since not all practices are linked to HES. Therefore, validation studies to confirm hospital admissions in THIN is an area that could be explored. In this context, validation of admission codes in THIN could be

conducted first (see Chapter 6), and then validation of other case definitions for PD could also be conducted (see Chapter 4).

7.8 Conclusion

This thesis set out to examine key outcomes in PD: hospitalisation and mortality. Work from my thesis has significantly contributed to the understanding of these outcomes of PD and prognosis of PD in the UK with important implications for clinicians, researchers and policy makers. Analysis of prospectively collected primary care data revealed that the trend in PD diagnosis decreased using stricter case definitions and stable using the broadest case definition. People with PD had higher rates of hospitalisation and mortality compared to controls without PD. Mortality rates in people with PD increased year on year following diagnosis of PD implying that mortality increased with longer duration of disease. Findings from this thesis also showed that the trend in mortality decreased over time (2007 to 2016) with rates of decline in controls without PD outpacing rates in people with PD resulting in a mortality gap. Future research investigating interventions that can slow disease progression and prevent modifiable causes of hospital admission in people with PD should be encouraged.

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Appendices

Appendix 2. Supplementary materials for chapter 2

Appendix 2-1: Published manuscript based on work done in chapter 2 of this thesis.

Parkinsonism and Related Disorders 71 (2020) 66–72

[redacted]

Review article

Factors associated with hospitalisation among people with Parkinson's disease – A systematic review and meta-analysis

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Appendix 2-2: PRISMA Checklist for Systematic Review on Factors associated with hospitalisation among people with Parkinson's disease.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	51
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	51 to 52
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	53
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	53
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	55 to 56
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	53 to 55
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	269 Appendix 2-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	55 to 57
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	57

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	59
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	57 to 58
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	59 to 61
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	59 to 61
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	61 to 64 Figure 2-1 Appendix 2-4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	62 to 63, 65, Figure 2-1(pg64) Table 2-2(pg65)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	69 to 70 Appendix 2-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	70 to 74 Appendix 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	70 to 74
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	71 to 73
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16].	NA

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	74 to 79
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	79 and 81
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	75 to 81
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Nil

Appendix 2-3: Medline search

1. Parkinson*.mp. [mp= title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. exp Parkinsonian Disorders/

3. 1 or 2

4. hospitalization*.mp. [mp= title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. hospitalisation*.mp.

6. (inpatient* adj3 care).mp. [mp= title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. admission*.mp.

8. Inpatients/

9. (Patient* adj3 admission*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. (Patient* adj3 readmission*).mp.

11. exp Hospitalization/

12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. 3 and 12

Appendix 2-4: Reasons for exclusion of excluded studies.

	Excluded Articles	Reasons for exclusion
1	Lannon et al 1986. Comprehensive care of the patient with Parkinson's disease.	Review article
2.	Trewin et al, 1997. Differences in drug prescribing patterns in elderly parkinsonian patients identified at hospital admission	Did not report reason for admission
3.	Parashos SA et al, 2002. Medical services utilization and prognosis in Parkinson disease: a population-based study	Did not report reason for admission
4.	Benbir G et al 2006. A hospital-based study: risk factors in development of motor complications in 555 Parkinson's patients on levodopa therapy	Reported risk factors
5.	Doux, MM, 1993. Management of the hospitalized Parkinson patient	Full text not found
6.	Escudero Torreila J, 1997. The medical care of patients with Parkinson's disease in a general hospital.	Full text not found
7.	Magdalinou K et al, 2007. Prescribing medications in Parkinson's disease (PD) patients during acute admissions to a district general hospital.	Did not report reason for admission
8.	Wood LD et al, 2010. Challenges of medication management in hospitalized patients with Parkinson's disease.	Commentary
9.	Aminoff MJ et al, 2011. Management of the hospitalized patient with Parkinson's disease: current state of the field and need for guidelines	Review
10.	Gerlach OH et al, 2011. Parkinson's disease and hospitalization: the need for guidelines.	Letter to the editor.
11.	Jones SL et al, 2011. Parkinson's disease in the acute hospital.	Review
12.	Donaldson S, 2010. Can we improve the inpatient care of those with Parkinson's disease?	Review
13.	Stickley L 2009. Parkinson disease: current evidence for acute care management	Review
14.	Eschie D, 2012. Patients with Parkinson's disease in hospital. [German].	Review
15.	Hobson DE et al, 2012. Healthcare utilization in patients with Parkinson's disease: a population-based analysis.	Did not report reason for hospitalisation.
16.	MacMahon MJ et al, 2012. Management of Parkinson's disease in the acute hospital environment.	Review
17.	Oguh O et al, 2012. Inpatient management of Parkinson disease: current challenges and future directions.	Review
18.	2013. Parkinson's inpatients criticise inflexible regimens in US study	Newsletter
19.	Gombert C et al, 2013. Parkinson's disease and intensive care: Specific issues? [French]	Review
20.	Arasalingam A et al, 2014. Reasons for Parkinson's disease admissions in a large inner-city hospital.	Letter to the editor
21.	Wijma-Vos L et al, 2014. Parkinson's short stay helps to better set medication: Brief intervention is possible alternative before final admission. [Dutch]	Dutch paper (review)

22.	Patel RS et al, 2017. Impact of Depression on Hospitalization and Related Outcomes for Parkinson's Disease Patients: A Nationwide Inpatient Sample-Based Retrospective Study.	Did not report reason for admission
23.	Paul SS et al, 2017. Fall-related hospitalization in people with Parkinson's disease.	Reported only falls
24.	Factor SA et al, 2000. Emergency department presentations of patients with Parkinson's disease.	Case series
25.	Muzerengi S et al, 2016. Review of interventions to reduce hospitalisation in Parkinson's disease.	review
26.	Queen V, 2017. Caring for patients with Parkinson's disease in general hospital settings	review
27.	Clarke C et al, 2015. Emergency admissions, hospital stays and in-hospital mortality higher in patients with Parkinson's disease.	News
28.	2015. Parkinson's carries higher risk of dying after admission.	News
29.	Straif-Bourgeois et al, 2015. Parkinson Disease Hospitalizations and Mortality in Louisiana, 1999-2012.	Did not report reason for admission
30.	Chang Y et al, 2016. Risk factors for pneumonia among patients with Parkinson's disease: A Taiwan nationwide population-based study.	Reported RFs for development of pneumonia
31.	DiBartolo M et al, 2017. Enhancing Care for Hospitalized Patients with Parkinson's Disease: Development of a Formal Educational Program for Nursing Staff.	Editorial
32.	Koay, L. Factors that lead to hospitalisation in patients with Parkinson disease-A systematic review.	Review
33.	Munim F, 2017. Management of inpatients with Parkinson's disease in the acute setting.	Algorithm
34.	M. Guttman, P.M. Slaughter, M.E. Theriault, D.P. DeBoer, C.D. Naylor, Parkinsonism in Ontario: comorbidity associated with hospitalization in a large cohort, Movement Disorders. 19(1) (2004) 49-53.	Did not report number admitted for what reason
35.	C. Vossius, O. Nilsen, J. Larsen, Parkinson's disease and hospital admissions: Frequencies, diagnoses and costs, Acta Neurologica Scandinavica. 121(1) (2010) 38-43.	Did not report number admitted for what reason
36.	B. Kelly, C. Blake, O. Lennon, Acute Hospital Admissions of Individuals with a Known Parkinson's Disease Diagnosis in Ireland 2009-2012: A Short Report. Journal of Parkinson Disease Print. 6(4) (2016) 709-716.	Did not report number admitted for what reason
37.	U. Lertxundi, A. Isla, M.A. Solinis, S.D. Echaburu, R. Hernandez, J. Peral-Aguirregoitia, J. Medrano, J.C. Garcia-Monco, Medication errors in Parkinson's disease inpatients in the Basque Country. Parkinsonism & Related Disorders, 36 (2017) 57-62.	Did not report number admitted for what reason
38.	H. Woodford, R. Walker, Emergency hospital admissions in idiopathic Parkinson's disease. Movement Disorders, 2005. 20(9): p. 1104-1108.	Did not report number admitted for what reason
39.	L. Shahgholi, S. De Jesus, S.S. Wu, Q.L. Pei, A. Hassan, M.J. Armstrong, D. Martinez-Ramirez, P. Schmidt, M.S. Okun, Hospitalization and rehospitalization in Parkinson disease	Did not report number admitted for

	patients: Data from the National Parkinson Foundation Centers of Excellence, Plos One. 12(7) (2017) 10.	what reason
40.	M. Harris,M. Fry, The utilisation of one district hospital emergency department by people with Parkinson's disease, Australasian Emergency Nursing Journal. 20(1) (2017) 1-5.	Did not report number admitted for what reason
41.	J.A Temlett, P.D. Thompson, Reasons for admission to hospital for Parkinson's disease. Internal Medicine Journal. 36(8) (2006) 524-526.	Did not report number admitted for what reason
42.	A. Merola, R.P. Sawyer, C.A. Artusi, R. Suri, Z. Berndt, J.R. Lopez-Castellanos, J. Vaughan, J.A. Vizcarra, A. Romagnolo, A.J. Espay, J.R. Lopez-Castellanos, Orthostatic hypotension in Parkinson disease: Impact on health care utilization. Parkinsonism & Related Disorders. 47 (2018) 45-49.	Did not report number admitted for what reason
43.	A. Mahajan, P. Balakrishnan, A. Patel, I. Konstantinidis, D. Nistal, N. Annapureddy, P. Poojary, G.N. Nadkarni, C. Sidiropoulos, Epidemiology of inpatient stay in Parkinson's disease in the United States: Insights from the Nationwide Inpatient Sample, Journal of Clinical Neuroscience. 31 (2016) 162-5.	Did not report number admitted for what reason
44.	R. Gil-Prieto, R. Pascual-Garcia, J. San-Roman-Montero, P. Martinez-Martin, J. Castrodeza-Sanz, A. Gil-de-Miguel, Measuring the Burden of Hospitalization in Patients with Parkinson's Disease in Spain, PLoS ONE [Electronic Resource]. 11(3) (2016) e0151563.	Did not report number admitted for what reason
45.	D. Martinez-Ramirez, L. Almeida, J.C. Giugni, B. Ahmed, M. Higuchi, C.S. Little, J.P. Chapman, C. Mignacca, A.W. Shukla, C.W. Hess, K.W. Hegland, M.S. Okun, Rate of aspiration pneumonia in hospitalized Parkinson's disease patients: a cross-sectional study. Bmc Neurology. 15 (2015) 6.	Did not report number admitted for what reason
46.	V. Low, Y. Ben-Shlomo, E. Coward, S. Fletcher, R. Walker, C.E. Clarke, Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009-2013. Parkinsonism & Related Disorders. 21(5) (2015) 449-54.	Did not report number admitted for what reason
47.	E.D. Louis, C. Henchcliffe, B.T. Bateman, C. Schumacher, Young-onset Parkinson's disease: hospital utilization and medical comorbidity in a nationwide survey, Neuroepidemiology. 29(1-2) (2007) 39-43.	Did not report number admitted for what reason
48.	O.H.H. Gerlach, M.P.G. Broen, P.H.M.F. van Domburg, A.J. Vermeij, W.E.J. Weber, Deterioration of Parkinson's disease during hospitalization: Survey of 684 patients. BMC Neurology. (2012) 13.	Did not report number admitted for what reason
49.	A.W. Willis, M. Schootman, R. Tran, N. Kung, B.A. Evanoff, J.S. Perlmutter, B.A. Racette, A.W. Willis, M. Schootman, R. Tran, N. Kung, B.A. Evanoff, J.S. Perlmutter, B.A. Racette, Neurologist-associated reduction in PD-related hospitalizations and health care expenditures, Neurology.	Did not report number admitted for what reason

	79(17) (2012) 1774-1780.	
50.	K.L. Chou, J. Zamudio, P. Schmidt, C.C. Price, S.A. Parashos, B.R. Bloem, K.E. Lyons, C.W. Christine, R. Pahwa, I. Bodis-Wollner, W.H. Oertel, O. Suchowersky, M.J. Aminoff, I.A. Malaty, J.H. Friedman, M.S. Okun, K.L. Chou, J. Zamudio, P. Schmidt, and C.C. Price, Hospitalization in Parkinson disease: a survey of National Parkinson Foundation Centers. Parkinsonism & Related Disorders. 17(6) (2011) 440-445.	Did not report number admitted for what reason
51.	M.Cosentino, E. Martignoni, D. Michielotto, D. Calandrella, G. Riboldazzi, C. Pacchetti, G. Frigo, G. Nappi, S. Lecchini, Medical healthcare use in Parkinson's disease: survey in a cohort of ambulatory patients in Italy. BMC Health Services Research. 5(1) (2005) 26.	Did not report number admitted for what reason
52.	R.W. Walker, J. Palmer, J. Stancliffe, B.H. Wood, A. Hand, W.K. Gray, Experience of care home residents with Parkinson's disease: Reason for admission and service use, Geriatrics & gerontology international. 14(4) (2014) 947-53.	Did not report number admitted for what reason
53.	C.P. Derry, K.J. Shah, L. Caie, C.E. Counsell, Medication management in people with Parkinson's disease during surgical admissions, Postgraduate Medical Journal. 86(1016) (2010) 334-337.	Did not report number admitted for what reason
54.	J. Martins, A. Rua, N.V. Cha, Hospital Mortality in Parkinson's Disease: Retrospective Analysis in a Portuguese Tertiary Centre, Acta Medica Portuguesa. 29(5) (2016) 315-318.	Did not report number admitted for what reason
55.	S. Muzerengi, C. Rick, I. Begaj, N. Ives, F. Evison, R.L. Woolley, C.E. Clarke, Coding accuracy for Parkinson's disease hospital admissions: implications for healthcare planning in the UK. Public Health. 146 (2017) 4-9.	Did not report number admitted for what reason
56.	P. Hobson, S. Roberts, G. Davies, The introduction of a Parkinson's disease email alert system to allow for early specialist team review of inpatients, BMC Health Services Research. 19(1) (2019) 271.	Did not report number admitted for what reason

Appendix 2-5: Newcastle **–** Ottawa Quality Assessment Scale

Appendix 2-5a: New - Ottawa quality assessment scale for Case-control studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate? "**1" OR "0"**
a) yes, with independent validation
b) yes, eg record linkage or based on self-reports
c) no description

2) Representativeness of the cases **"1" 0R "0"**
a) consecutive or obviously representative series of cases
b) potential for selection biases or not stated

3) Selection of Controls **"1" 0R "0"**
a) community controls
b) hospital controls
c) no description

4) Definition of Controls **"1" OR "0"**
a) no history of disease (endpoint)
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis "**1"OR "2" OR "0"**
a) study controls for_____(Select the most important factor.)
b) study controls for any additional factor (This criterion could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (e.g surgical records) **"1" 0R "0"**
b) structured interview where blind to case/control status
c) interview not blinded to case/control status
d) written self-report or medical record only
e) no description

2) Same method of ascertainment for cases and controls **"1" OR "0"**
a) yes
b) no

3) Non-Response rate "**1" OR "0"**
a) same rate for both groups
b) non respondents described
c) rate different and no designation

Appendix 2-5b: New – Ottawa quality assessment scale for Cohort Studies

Note: A study can be awarded a maximum of one for each numbered item within the Selection and Outcome categories. A maximum of two can be given for Comparability

Selection

1) Representativeness of the exposed cohort **"1" OR "0"**
- a) truly representative of the average_____(describe) in the community
- b) somewhat representative of the average_____in the community
- c) selected group of users e.g., nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort **"1" OR "0"**
- a) drawn from the same community as the exposed cohort
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure **"1" OR "0"**
- a) secure record (e.g., surgical records)
- b) structured interview
- c) written self-report
- d) no description

4) Demonstration that outcome of interest was not present at start of study
- a) yes
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for_____(select the most important factor)
b) study controls for any additional factor (This criterion could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
- a) independent blind assessment
- b) record linkage
- c) self-report
- d) no description

2) Was follow-up long enough for outcomes to occur
- a) yes (select an adequate follow up period for outcome of interest)
- b) no

3) Adequacy of follow up of cohorts
- a) complete follow up - all subjects accounted for
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > _____ % (select an adequate %) follow up, or description provided of those lost)
- c) follow up rate <_____% (select an adequate %) and no description of those lost
- d) no statement

Appendix 2-5c: Coding manual for case control studies

Selection

1) Is the Case Definition Adequate?

a) Requires some independent validation (e.g., >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records)
b) Record linkage (e.g., ICD codes in database) or self-report with no reference to primary record
c) No description

2) Representativeness of the Cases

a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g., random sample)
b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (i.e., same community as cases and would be cases if had outcome)
b) Hospital controls, within same community as cases (i.e., not another city) but derived from a hospitalised population
c) No description

4) Definition of Controls

a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.
b) No mention of history of outcome

Comparability

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 scores can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = 1 Other controlled factor = 1

Exposure

1) Ascertainment of Exposure
Allocation of score as per rating sheet

2) Non-Response Rate
Allocation of scores as per rating sheet

Appendix 2-5d: Coding manual for Cohort studies

Selection

1) Representativeness of the Exposed Cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health-oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen).

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of score as per rating sheet

3) Ascertainment of Exposure

Allocation of score as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a score.

Comparability

1) Comparability of Cohorts on the Basis of the Design or Analysis

A maximum of 2 can be allotted in this category
Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = 1, Other controlled factors = 1

Outcome

1) Assessment of Outcome

For some outcomes (e.g., fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)
b) Record linkage (e.g., identified through ICD codes on database records)
c) Self-report (i.e., no reference to original medical records or x-rays to confirm the outcome)
d) No description.

2) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins (e.g., 5 yrs. for exposure to breast implants)

3) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of scores as per rating sheet.

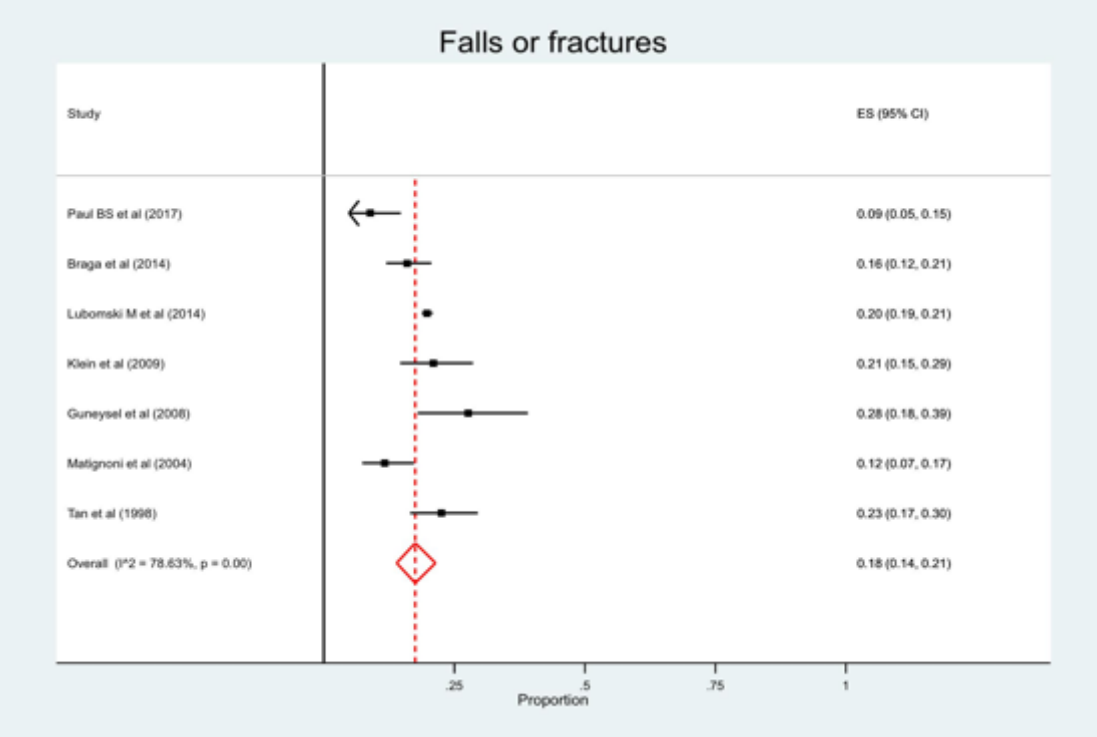
Appendix 2-6: Results of Meta-analysis (pooled prevalence of common reasons for admission and study bias of the articles).

1. Falls/Fractures

Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.09	0.05	0.15
Braga et al (2014)	0.16	0.12	0.21
Lubomski M et al (20	0.20	0.19	0.21
Klein et al (2009)	0.21	0.15	0.29
Guneysel et al (2008	0.28	0.18	0.39
Matignoni et al (200	0.12	0.07	0.17
Tan et al (1998)	0.23	0.17	0.30
Random pooled ES	0.18	0.14	0.21

Heterogeneity chi^2 = 28.08 (d.f. = 6) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 78.63%
Estimate of between-study variance Tau^2 = 0.01

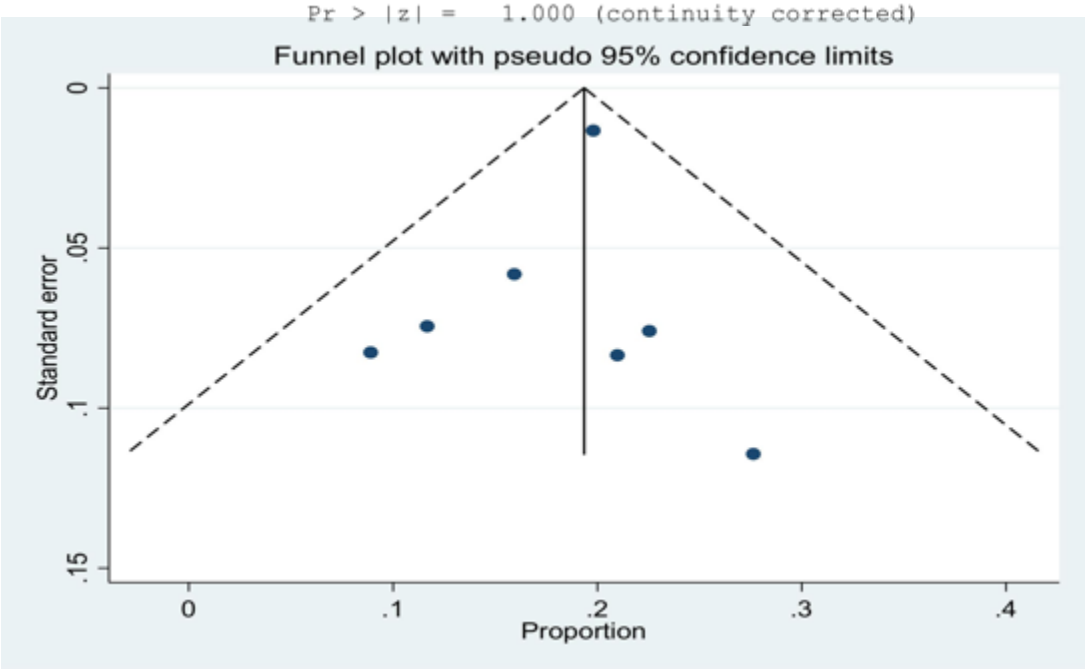
Test of ES=0 : z= 15.98 p = 0.00



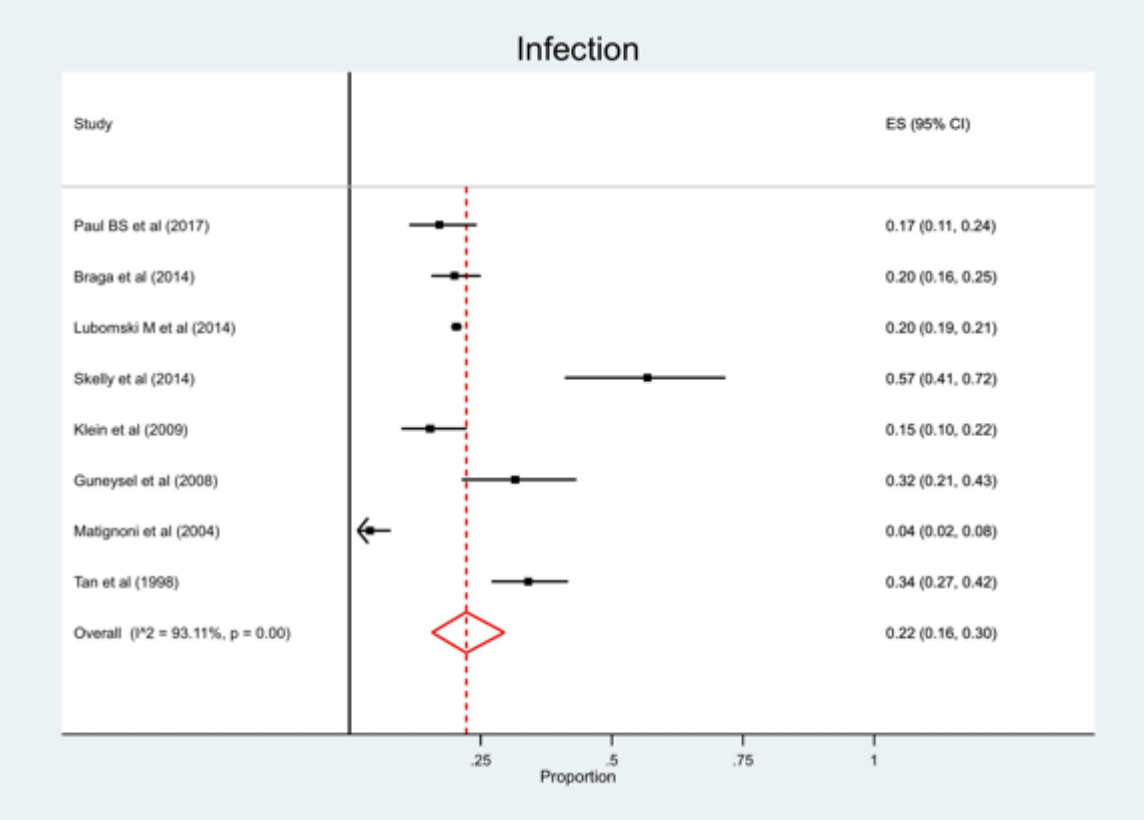
```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  7                                  Root MSE      =    .8303
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2013329	.0143125	14.07	0.000	.1645413	.2381244
bias	-.3423053	.4412579	-0.78	0.473	-1.476595	.7919843

```
Test of H0: no small-study effects          P = 0.473

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =      -1
         Std. Dev. of Score =    6.66
          Number of Studies =       7
                          z  =   -0.15
                    Pr > |z| =   0.881
                          z  =    0.00 (continuity corrected)
                    Pr > |z| =   1.000 (continuity corrected)
```



2. Infections (UTI & Pneumonia)



Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.17	0.11	0.24
Braga et al (2014)	0.20	0.16	0.25
Lubomski M et al (20	0.20	0.19	0.21
Skelly et al (2014)	0.57	0.41	0.72
Klein et al (2009)	0.15	0.10	0.22
Guneysel et al (2008	0.32	0.21	0.43
Matignoni et al (200	0.04	0.02	0.08
Tan et al (1998)	0.34	0.27	0.42
Random pooled ES	0.22	0.16	0.30

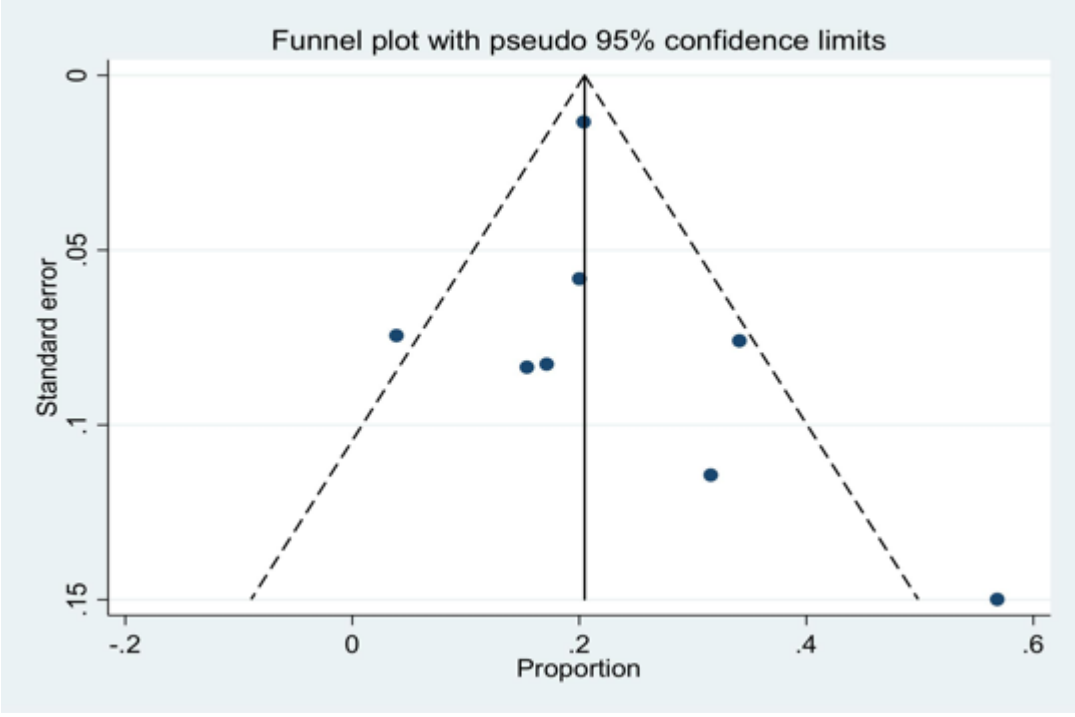
Heterogeneity chi^2 = 101.61 (d.f. = 7) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 93.11%
Estimate of between-study variance Tau^2 = 0.05

Test of ES=0 : z= 10.68 p = 0.00

```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  8                                  Root MSE      =     1.57
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1946493	.0263049	7.40	0.000	.1302834	.2590152
bias	.4245185	.7611404	0.56	0.597	-1.437925	2.286962

```
Test of H0: no small-study effects          P = 0.597

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =       8
         Std. Dev. of Score =    8.08
          Number of Studies =       8
                          z  =    0.99
                    Pr > |z| =   0.322
                          z  =    0.87 (continuity corrected)
                    Pr > |z| =   0.386 (continuity corrected)
```

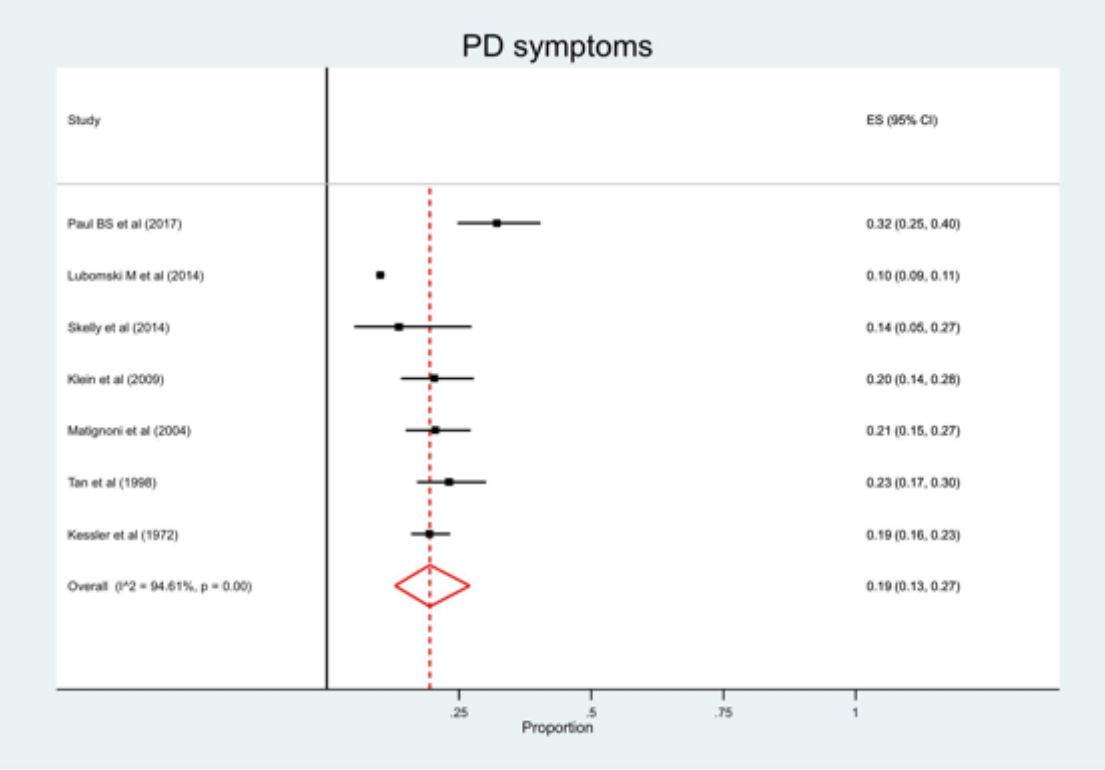


3. Worsening motor symptoms of PD

Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.32	0.25	0.40
Lubomski M et al (20	0.10	0.09	0.11
Skelly et al (2014)	0.14	0.05	0.27
Klein et al (2009)	0.20	0.14	0.28
Matignoni et al (200	0.21	0.15	0.27
Tan et al (1998)	0.23	0.17	0.30
Kessler et al (1972)	0.19	0.16	0.23
Random pooled ES	0.19	0.13	0.27

Heterogeneity chi^2 = 111.22 (d.f. = 6) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 94.61%
Estimate of between-study variance Tau^2 = 0.05

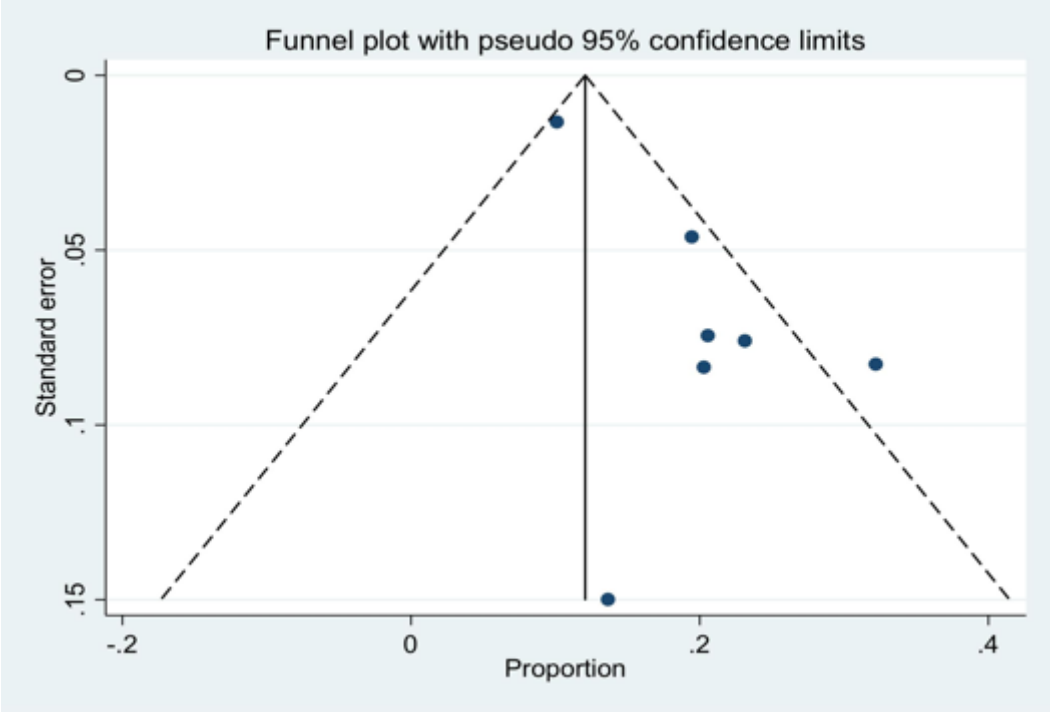
Test of ES=0 : z= 9.23 p = 0.00



```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  7                                  Root MSE      =    .8907
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0802673	.0152701	5.26	0.003	.0410141	.1195204
bias	1.780277	.4757433	3.74	0.013	.55734	3.003214

```
Test of H0: no small-study effects           P = 0.013

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =      -1
         Std. Dev. of Score =    6.66
          Number of Studies =       7
                          z  =   -0.15
                    Pr > |z| =   0.881
                          z  =    0.00 (continuity corrected)
                    Pr > |z| =   1.000 (continuity corrected)

.
```



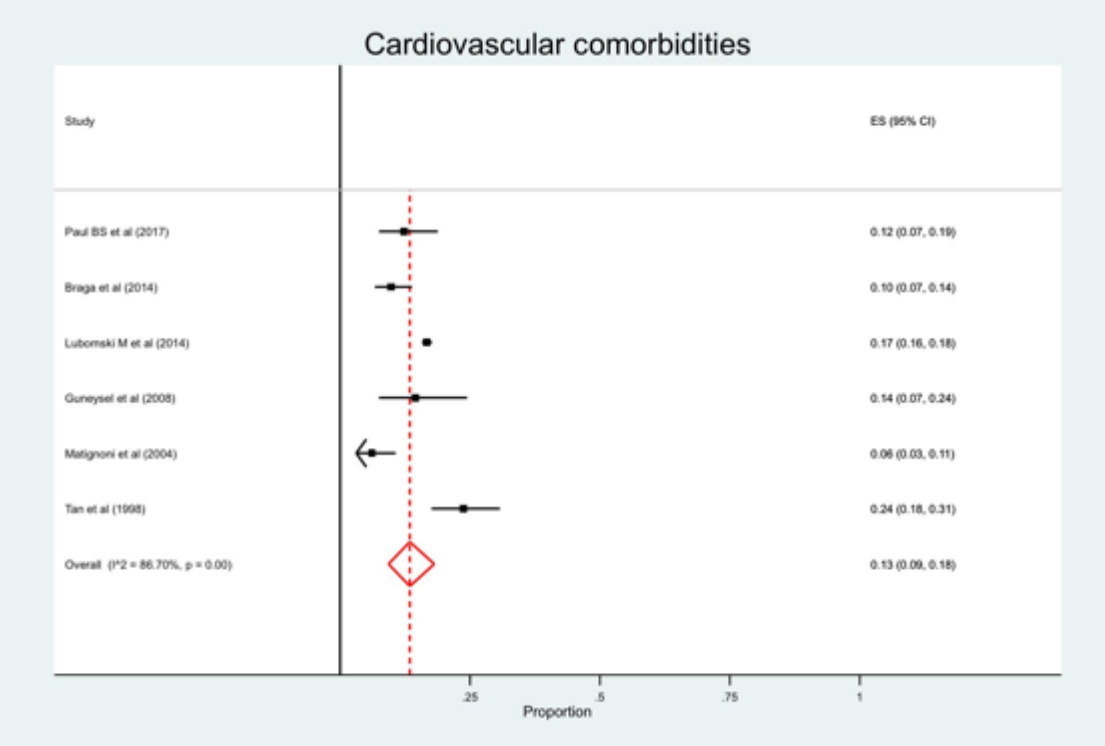
4. Cardiovascular co-morbidities

Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.12	0.07	0.19
Braga et al (2014)	0.10	0.07	0.14
Lubomski M et al (20	0.17	0.16	0.18
Guneysel et al (2008	0.14	0.07	0.24
Matignoni et al (200	0.06	0.03	0.11
Tan et al (1998)	0.24	0.18	0.31
Random pooled ES	0.13	0.09	0.18

Heterogeneity chi^2 = 37.60 (d.f. = 5) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 86.70%
Estimate of between-study variance Tau^2 = 0.02

Test of ES=0 : z= 10.41 p = 0.00

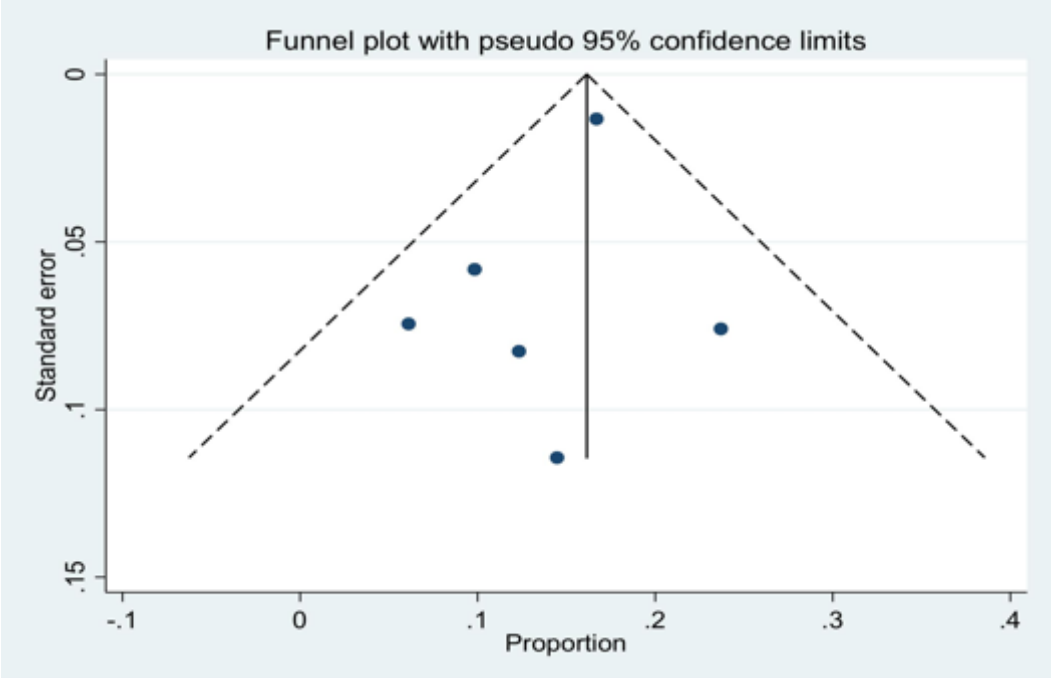
.



```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  6                                  Root MSE      =    .9341
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1732593	.0163707	10.58	0.000	.1278071	.2187116
bias	-.5475014	.5392384	-1.02	0.367	-2.044667	.9496645

```
Test of H0: no small-study effects          P = 0.367

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =      -1
        Std. Dev. of Score =    5.32
         Number of Studies =       6
                         z  =   -0.19
                  Pr > |z|  =   0.851
                         z  =    0.00 (continuity corrected)
                  Pr > |z|  =   1.000 (continuity corrected)
```

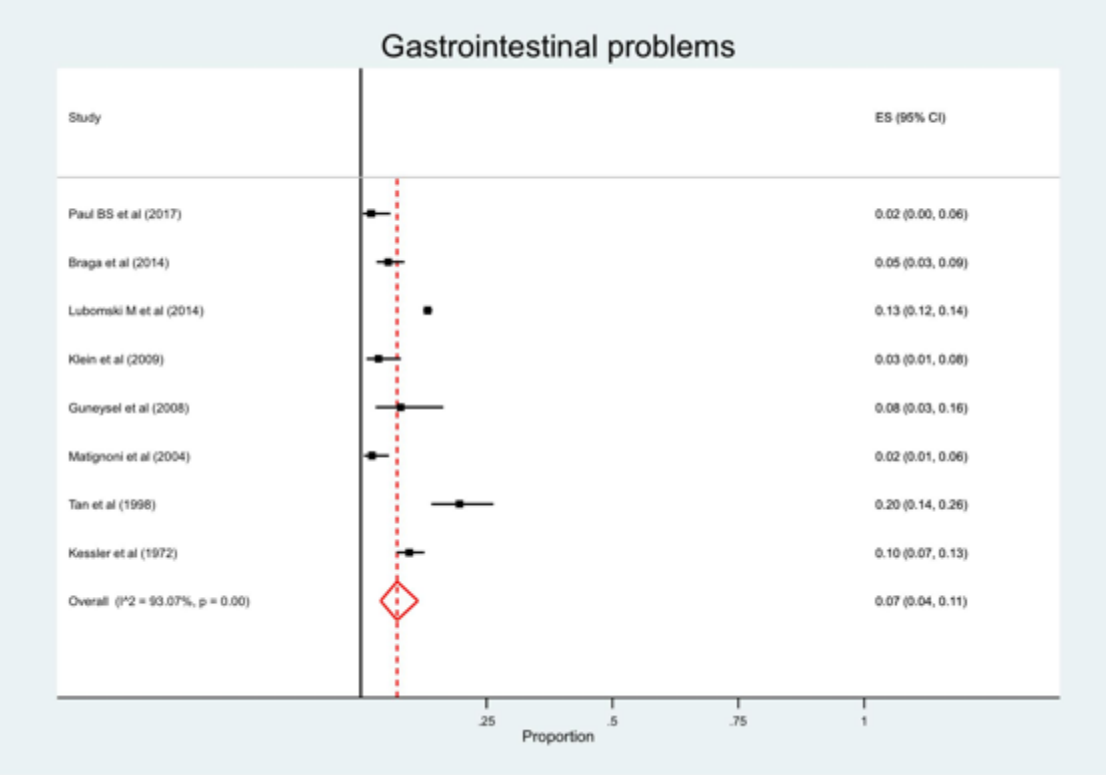


5.Gastrointestinal problems

Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.02	0.00	0.06
Braga et al (2014)	0.05	0.03	0.09
Lubomski M et al (20	0.13	0.12	0.14
Klein et al (2009)	0.03	0.01	0.08
Guneysel et al (2008	0.08	0.03	0.16
Matignoni et al (200	0.02	0.01	0.06
Tan et al (1998)	0.20	0.14	0.26
Kessler et al (1972)	0.10	0.07	0.13
Random pooled ES	0.07	0.04	0.11

Heterogeneity chi^2 = 100.95 (d.f. = 7) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 93.07%
Estimate of between-study variance Tau^2 = 0.04

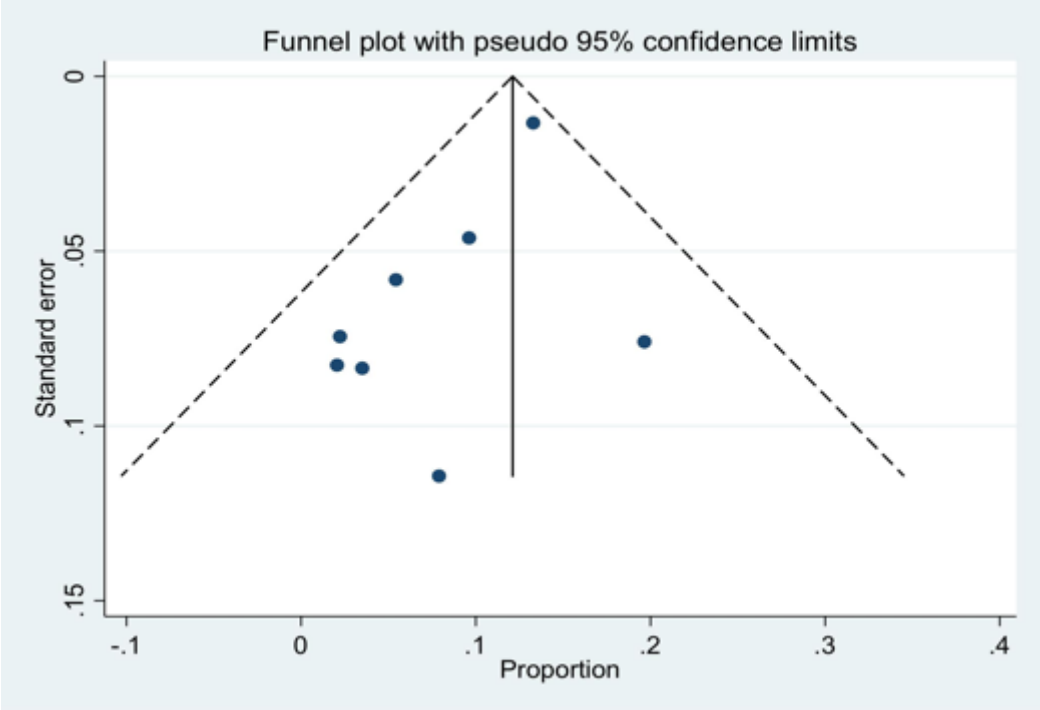
Test of ES=0 : z= 6.67 p = 0.00



```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  8                                  Root MSE      =    .8266
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.145249	.0142487	10.19	0.000	.1103836	.1801144
bias	-.9930237	.4251401	-2.34	0.058	-2.033304	.0472566

```
Test of H0: no small-study effects          P = 0.058

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =      -4
        Std. Dev. of Score =    8.08
       Number of Studies =       8
                        z  =   -0.49
                  Pr > |z| =   0.621
                        z  =    0.37 (continuity corrected)
                  Pr > |z| =   0.711 (continuity corrected)
```

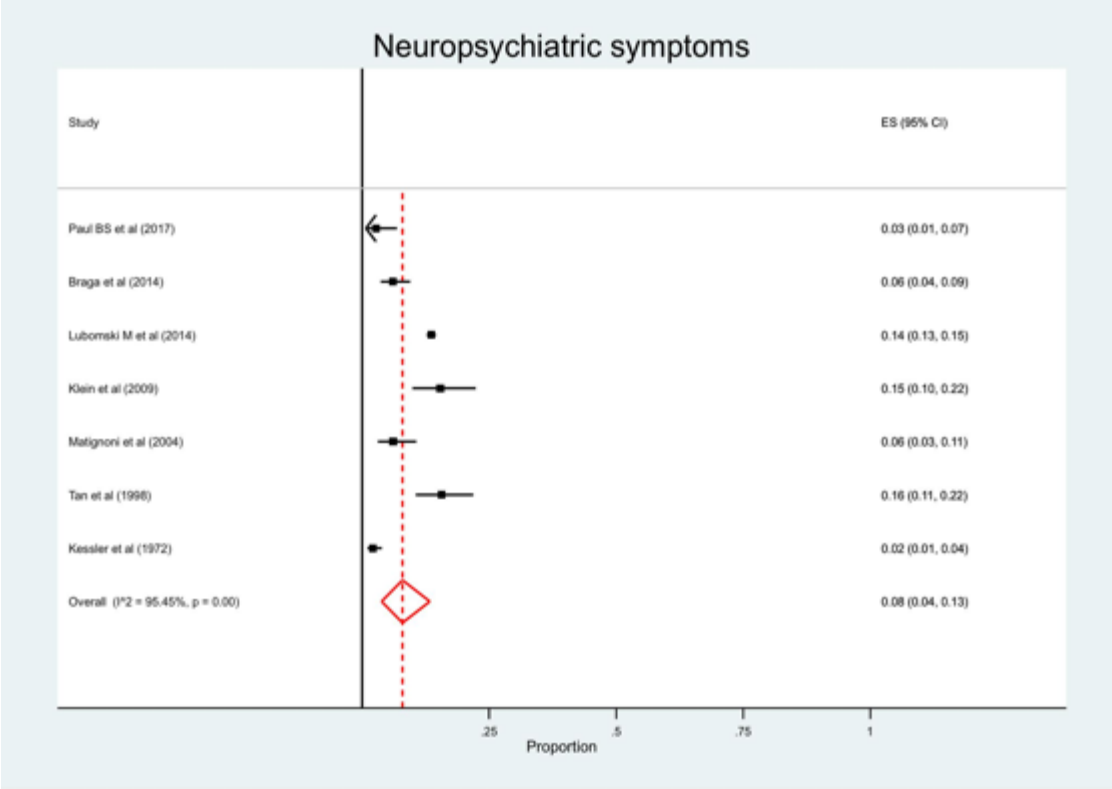


6. Neuropsychiatric complications

Study	ES	[95% Conf.	Interval]
Paul BS et al (2017)	0.03	0.01	0.07
Braga et al (2014)	0.06	0.04	0.09
Lubomski M et al (20	0.14	0.13	0.15
Klein et al (2009)	0.15	0.10	0.22
Matignoni et al (200	0.06	0.03	0.11
Tan et al (1998)	0.16	0.11	0.22
Kessler et al (1972)	0.02	0.01	0.04
Random pooled ES	0.08	0.04	0.13

Heterogeneity chi^2 = 131.81 (d.f. = 6) p = 0.00
I^2 (variation in ES attributable to heterogeneity) = 95.45%
Estimate of between-study variance Tau^2 = 0.05

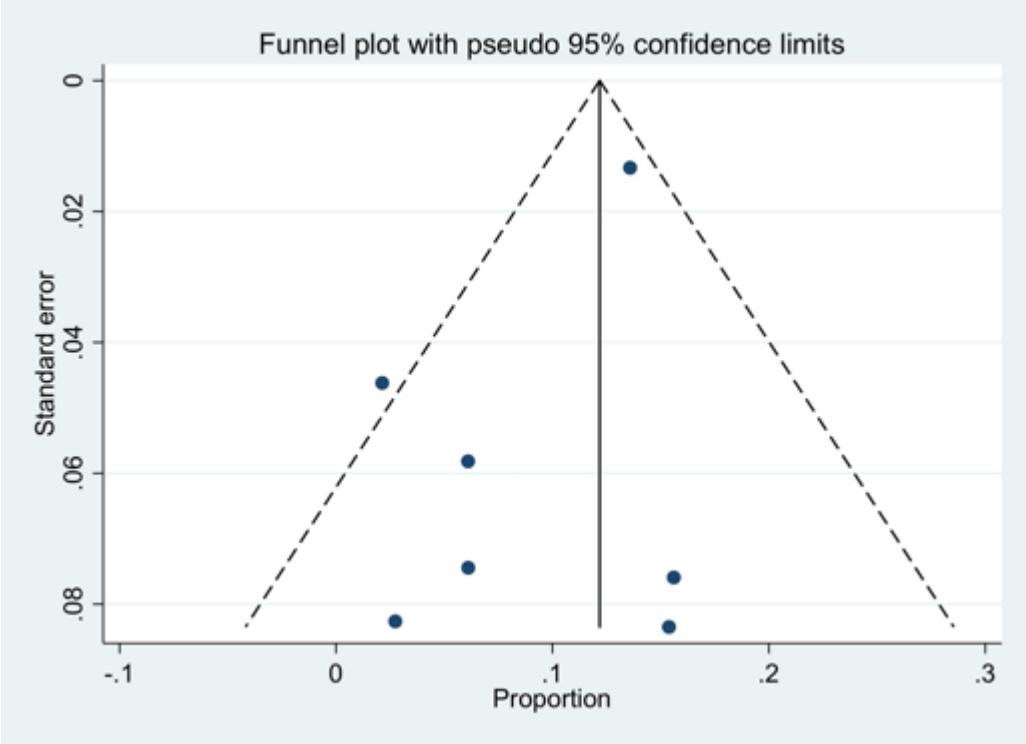
Test of ES=0 : z= 5.77 p = 0.00



```
Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  7                                  Root MSE      =    1.08
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1461752	.0191666	7.63	0.001	.0969059	.1954444
bias	-1.042285	.6080669	-1.71	0.147	-2.605371	.5208002

```
Test of H0: no small-study effects          P = 0.147

. metabias _ES _seES, beg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard err
> or

  adj. Kendall's Score (P-Q) =       1
        Std. Dev. of Score =    6.66
       Number of Studies =       7
                        z  =    0.15
                  Pr > |z| =   0.881
                        z  =    0.00 (continuity corrected)
                  Pr > |z| =   1.000 (continuity corrected)
```



Appendix 2-7: General characteristics of excluded papers which provided no data for analysis but had reasons for admission.

Author	Year	Country	Study design	Aim of study	Main reasons for admission reported
Hobson et al	2019	United Kingdom	Retrospective	Describe method, introduction and economic costs of introducing an e-alert system for PD specialist team for PwPD* attending ED.	Falls/fractures, UTI, feeling unwell, medication problems.
Merola et al	2018	USA	Retrospective	Evaluate the effect of orthostatic hypotension on health care utilization among PwPD	Falls, neuropsychiatric complications and Rehabilitation
Shahgholi et al	2017	USA	Prospective	To evaluate hospital admissions and identify associated factors.	Infections, cardiovascular and respiratory co-morbidities, cancer.
Muzerengi et al	2017	United Kingdom	Retrospective	To estimate the number of PD admissions to a large Birmingham hospital and assess the coding accuracy.	Infections, falls, fractures, cardiovascular and circulatory disorders.
Lertxundi et al	2017	Spain	Retrospective	To evaluate the prevalence of medication errors.	PD-related complications, UTI, Pneumonia
Harris M et al	2017	Australia	Retrospective	To describe trends and characteristics of older PwPD presenting to ED.	Falls, pain, infection and general review.
Martins J et al	2016	Portugal	Retrospective	To identify inpatient mortality (reasons for hospital admission and cause of death) in PwPD admitted to a tertiary hospital.	Pneumonia, sepsis from UTI, Stroke, End-stage cancer
Mahajan et al	2016	USA	Retrospective	To confirm that care on a specialist in-patient PD Unit (SPDU) would improve outcomes of urgent medical care among PwPD.	Pneumonia, UTI, Sepsis, Aspiration pneumonitis, Rehabilitation, CCF.
Kelly B et al	2016	Republic of Ireland	Retrospective	To outline preventable admissions among PwPD in order to inform primary care initiatives that will help maintain their health status.	Respiratory diseases-Pneumonia, Pneumonitis due to swallowing problems, COPD, UTI, Fracture.

PwPD People with Parkinson's disease

Appendix 2-7: General characteristics of excluded papers which provided no data for analysis but had reasons for admission.

Author	Year	Country	Study design	Aim of study	Main reasons for admission reported
Gil-Prieto et al	2016	Spain	Retrospective	To estimate the incidence of hospitalizations among PwPD from 1997 to 2012 in Spain.	Infections and parasitic diseases, Neoplasms, Endocrine, nutritional, metabolic.
Martinez et al	2015	USA	Retrospective	To evaluate the frequency of aspiration events in PwPD during hospital encounters.	Fall/fractures, Pulmonary, general medical and gastrointestinal problems.
Low et al	2015	United Kingdom	Retrospective	To determine the magnitude and direct healthcare costs and reasons for admission and mortality among PwPD in order to recommend preventive initiatives to reduce hospitalizations.	PD related problems, UTI, Pneumonia, Septicaemia, cellulitis, Delirium, Syncope, Orthostatic hypotension.
Walker et al	2014	United Kingdom	Retrospective	To establish the needs of care home residents with PD.	Falls, confusion, decreased mobility, fractures, UTI, Swallowing problems, Pneumonia.
Gerlach O et al	2013	The Netherlands	Prospective	To analyse prospectively whether or not there is deterioration of motor function at discharge of hospitalized PwPD compared to admission, and if so, assess its severity and related factors.	Orthopaedic reviews: Hip fracture and hip replacement surgery; Neurology: PD medication errors, worsening PD symptoms.
Willis A et al	2012	USA	Retrospective	To establish that greater familiarity with neurologic disease gained specialty training would lead to a reduction in PD related morbidity and improvement in outcomes.	PD-related problems: neurodegenerative disease, psychosis, UTI
Chou K et al	2011	USA	Prospective	To explore current practises and opinions at National Parkinson foundation centres regarding hospitalization of PwPD.	Elective surgery, falls/fractures, Infections, aspiration pneumonia, medication issues.

Appendix 2-7: General characteristics excluded papers which provided no data for analysis but had reasons for admission

Author	Year	Country	Study design	Aim of study	Main reasons for admission reported
Vossius C et al	2010	Norway	Prospective	To give an estimate on the incremental economic impact of hospitalization in PD to the society.	Cardiovascular disorders, Pneumonia, cancer, trauma, genitourinary tract disorders.
Derry C et et al	2010	United Kingdom	Retrospective	To examine the pharmacological management of PwPD during surgical admissions.	Missed doses of medication, orthopaedic surgeries for fractures.
Louis E et al	2007	USA	Retrospective	To use a large administrative database to compare hospital utilization and outcomes among people with young onset PD and controls.	UTI, pneumonia, rehabilitation, psychosis, fractures.
Temlett M et al	2006	Australia	Retrospective	To compare the number of admissions related to management of primary motor disorder with the number admitted for secondary problems such as falls, cognitive disorders, drug side-effects and the complications of immobility	Fractures/falls, Pneumonia, cardiovascular, GIT and urinary disorders, motor fluctuations and dyskinesias, confirm diagnosis and levodopa responsiveness.
Woodford H et al	2005	United Kingdom	Retrospective	To try and understand for which patients, and what reasons, emergency admission is required.	Infective disease, pneumonia, UTI, cardiovascular disorders, falls, decreased mobility/dyskinesia, fractures, orthostatic hypotension.
Consentino M et al	2005	Italy	Retrospective	To assess the reasons for medical healthcare use among PwPD and determine the relationship between health care use and pattern of anti-parkinsonian drug medications.	Rehabilitation, chest pain, fractures, falls, pneumonia, dyskinesias, dysphagia.
Guttmann et al	2004	Canada	Retrospective	To evaluate the diagnosis most responsible for hospitalization in a large cohort of patients with Parkinsonism.	PD related symptoms, Pneumonia, cardiovascular, cerebrovascular and GIT disorders.

Appendix 2-8: All reasons for admission.

Study Reasons for hospitalization	Paul BS et al (2017)	Lubomski et al (2014)	Braga et al (2014)	Skelly et al (2014)	Klein et al (2009)	Guneysel et al (2008)	Matignoni et al (2004)	Tan et al (1998)	Kessler et al (1972)
Falls & fractures	+	+	+		+	+	+	+	
Infections (UTI & Pneumonia)	+	+	+	+	+	+	+	+	
Motor complications	+	+		+	+		+	+	+
CVS co-morbidities	+	+	+			+	+	+	
Neuropsychiatric problems	+	+	+		+		+	+	+
CVD/Stroke	+	+	+		+	+	+		
GIT problems	+	+	+		+	+	+	+	+
Genito-urinary problems	+		+				+	+	+
Neoplasia		+	+				+	+	
Surgical Problems							+	+	

+ presence of reason/cause of admission

Appendix 2-8: All reasons for admission

Study Reasons for hospitalization	Paul BS et al (2017)	Lubomski et al (2014)	Braga et al (2014)	Skelly et al (2014)	Klein et al (2009)	Guneysel et al (2008)	Matignoni et al (2004)	Tan et al (1998)	Kessler et al (1972)
Encephalo-pathy (delirium & electrolyte imbalance)	+	+	+		+	+			+
Dementia		+			+			+	
Syncope/ Orthostatic Hypotension		+	+	+	+		+		+
Other neurological problems	+		+		+				
Others (unmentioned)	+		+	+	+				

+ presence of reason/cause of admission

Appendix 2-9: Quality assessment of included studies using the Newcastle-Ottawa scale.

Study ID	Reference	Case definition	Represen tation	Control selection	Control definition	Comparability	Exposure ascertain-ment	Same method of ascertainment	Response rate	Total score
Case-Control										
1	Lubomski et al	b0	a1	b0	a1	a1b1 age, gender	a1	b0	b0	5
2	Braga et al	a1	a1	b0	a1	a1b1 age,sex,ethnicity & same admission year	a1	a1	b0	7
3	Kessler et al	a1	a1	a1	a1	a0b0	a1	a1	a1	7

Cohort Studies Study ID	Reference	Represen tation of exposed cohort	Selection of non-exposed cohort	Exposure Ascertain ment	Study outcome was not present at the start of study	Comparability	Outcome assessment	Was follow-up adequate to assess outcome	Adequacy of follow-up of cohort	Total score
4	Paul BS et al	a1	c0	a1	a1	a0b0	a1	b0	a1	5
5	Skelly et al	a1	c0	a1	a1	a0b0	a1	b0	d0	4
6	Klein et al	a1	a1	a1	a1	a1b0	a1	a1	a1	8
7	Guneysel et al	a1	c0	a1	a1	a0b0	a1	b0	a1	5
8	Matignoni et al	a1	c0	a1	a1	a0b0	a1	b0	a1	5
9	Tan et al	a1	c0	a1	a1	a0b0	a1	b0	a1	5

Appendix 3. Supplementary materials for chapter 3

Appendix 3-1: Ethical approval.

SRC Feedback

Researcher Name: Anette Schrag
Organisation: University College London
SRC Reference Number: 19THIN034
Date: 27th June 2019
Study title: Factors associated with hospitalisation and mortality among people with Parkinson's disease: Analysis of a large primary care dataset.

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_19THIN034_v1_08-05-2019	1	08/05/2019
SRC_19THIN034_researcher_response		

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Research Ethics Committee (REC) know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA for us to advise the SRC and your reference number to be closed.

References to all published studies are added to IQVIA's online bibliography enabling other researchers to become aware of your work. To identify your study as using the THIN database, this statement **must** be included in all publication (i.e. slides, posters, manuscripts, articles, abstracts etc):

"THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA"

"This work uses de-identified data provided by patients as a part of their routine primary care"

In addition, studies that use THIN-HES linked data **must** include the following:

"Copyright © 2019, re-used with the permission of The Health & Social Care Information Centre. All rights reserved"

I wish you and your team all the best with the study progression.

[redacted]

Mustafa Dungarwalla
SRC Coordinator

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SRC
Scientific Review Committee

Appendix 3-2: Structure of Read codes

Chapter	Contents
0	Occupations
1	History & symptoms
2	Examination signs
3	Diagnostic procedures
4	Laboratory procedures
5	Radiology & physics in medicine
6	Preventative procedures
7	Operations and procedures
8	Other therapeutic procedures
9	Administration
A	Infections and parasitic diseases
B	Neoplasms
C	Endocrine, nutrition, metabolic and immunity disorders
D	Diseases of blood and blood forming organs
E	Mental disorders
F	Nervous system and sense organ disease
G	Circulatory system diseases
H	Respiratory system diseases
J	Digestive system diseases
K	Genitourinary system diseases
L	Complications of pregnancy, childbirth and puerperium
M	Skin & subcutaneous tissues diseases
N	Musculoskeletal and connective diseases
P	Congenital anomalies
Q	Perinatal conditions
R	[D] Symptoms, signs and ill-defining conditions
S	Injury & poisoning
T	Causes of injury and poisoning
U	[X] External causes of morbidity and mortality
Z	Unspecified conditions

Appendix 3-3: Record statement checklist.

	STROBE items	**Location in the thesis where items have been reported**	**RECORD items**	**Location in thesis where items have been reported**
Title and abstract				
	(A) Indicate the study's design with a commonly used term in the title or the abstract. (B) Provide in the abstract an informative and balanced summary of what was done and what was found.	(A) Page 1- Title page (B) Page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Page 1- Title page Page 1- Title page
Introduction				
Background rationale	Explain the scientific background and rationale for the investigation being reported	Chapter 4: Section 4.2 Chapter 5: Section 5.2 Chapter 6: Section 6.2		
Objectives	State specific objectives, including any prespecified hypotheses	Chapter 4: Section 4.3 Chapter 5: Section 5.3 and 5.4 Chapter 6: Section 6.3 and 6.4		
Methods				
Study design	Present key elements of the study design early in the paper.	Chapter 4: Section 4.4 Chapter 5: Section 5.5 Chapter 6: Section 6.5		
Setting	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	Chapter 4: Section 4.4 Chapter 5: Section 5.5 Chapter 6: Section 6.5		

Participants	(A) Cohort study: Give the eligibility criteria, and the sources and the methods of selection of participants. Describe methods of selection of participants. Describe methods of follow-up.	Chapter 4: Section 4.4.2, 4.4.3 and 4.4.4 Chapter 5: Section 5.5.2, 5.5.3 and 5.5.4 Chapter 6: Section 6.5.2, 6.5.3 and 6.5.4	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	Chapter 4: Section 4.4.4 Chapter 5: Section 5.5.4 and 5.5.4.3 Chapter 6: Section 6.5.2 Described in Chapter 4 for all 3 chapters: Section 4.8
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Chapter 4: Section 4.6 and 4.7 Chapter 5: Section 5.5.4.5 and 5.5.4.6 Chapter 6: Section 6.5.5 and 6.5.6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix 4-1 for both Chapter 4 and 5. Appendix 6-1
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Chapter 4: Section 4.4.1 Chapter 5: Section 5.5.1 Chapter 6: Section 6.5.1 (See also Chapter 3 for all 3 studies.)		
Bias	Describe any efforts to address potential sources of bias.	Chapter 4: Section 4.5 Chapter 5: Section 5.5.3 Chapter 6: Section 6.5.3		
Study size	Explain how the study size was arrived at	Chapter 4: Section 4.4 Chapter 5: Section 5.5		

		Chapter 6: Section 6.5		
Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	Chapter 4: Section 4.6 Chapter 5 Section 5.6 Chapter 6: Section 6.5 and 6.8.2		
Statistical methods	(A) Describe all statistical methods, including those used to control for confounding. (B) Describe any methods usd to examine subgroups and interactions. (C) Explain how missing data were addressed. (D) Cohort study: If applicable, explain how loss to follow-up was addressed. (E) Describe any sensitivity analyses	Chapter 4: Section 4.7 Chapter 5: Section 5.6 Chapter 6: Section 6.5		
Data access and cleaning methods			RECORD 12:1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Described in chapter 3 for all three studies. Chapter 4: Section 4.4.4 and 4.5 Chapter 5: Section 5.5.3 and 5.5.4.2 Chapter 6: Section 6.5.3 and 6.5.4
Results				
Participants	(A) Report the number of individuals at each stage of the study (for example numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (B) Give reasons for non-participation at each stage. (C) Consider use of a flow diagram.	Chapter 4: Section 4.4.4 and 4.10 and 4.10.1 Chapter 5: Section 5.5.4.2 and 5.8.1 Figures 5-1 and 5-2 Chapter 6: Section 6.5.4 Figure 6-1	RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Chapter 4: Section 4.4.4 and 4.10 and 4.10.1 Chapter 5: Section 5.5.4.2 and 5.8.1 Figures 5-1 and 5-2 Chapter 6: Section 6.5.4 Figure 6-1

Descriptive data	(A) Give characteristics of study participants (for example demographic, clinical, social) and information on exposures and potential confounders. (B) Indicate the number of participants with missing data for each variable of interest. (C) Cohort study: summarise follow-up time (for example average and total amount)	Chapter 4: Section 4.10.1 Chapter 5: Section 5.8.1 Chapter 6: Section 6.8.1		
Outcome data	Cohort study: Report numbers of outcome events or summary measures over time.	Chapter 4: Section 4.10.1 Chapter 5: Section 5.8.1 Table 5-1 Chapter 6: Section 6.8.1 and Table 6-1		
Main results	(A) Give unadjusted estimates and if applicable, confounders adjusted estimates and their precision (for example 955 confidence interval). Make clear which confounders were adjusted for and why they were included. (B) Report category boundaries when continuous variables were categorised. (C) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	Chapter 4: Section 4.10.1 to 4.10.7 Chapter 5: Section 5.8.2 and 5.8.3 and 5.8.5 Table 5-2 Chapter 6: Section 6.8.2		
Other analyses	Report other analyses done for example analyses of subgroups and interactions, and sensitivity analyses.	Chapter 4: Section 4.10.2 to 4.10.7 Chapter 5: Section 5.8.4 Chapter 6: Section 6.8.3 to 6.8.5		
Discussion				
Key results	Summarise key results with reference to study objectives.	Chapter 4: Section 4.11.1 Chapter 5: Section 5.9.1 Chapter 6: Section 6.9.1		
Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	Chapter 4: Section 4.12 Chapter 5:	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the	Chapter 4: Section 4.12

	direction and magnitude of any potential bias.	Section 5.10 Chapter 6: Section 6.10	specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being to the study being reported.	Chapter 5: Section 5.10 Chapter 6: Section 6.10
Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.	Chapter 4: Section 4.11.2 Chapter 5: Section 5.9.2 Chapter 6: Section 6.9.2		
Generalisability	Discuss the generalisability (external validity) of the study results)	Chapter 4: Section 4.11.24.13 Chapter 5: Section 5.9.2 and 5.11 Chapter 6: Section 6.9.2 and 6.11		

This checklist was adapted from the version described in: Benchimol EL, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al (2015). The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement (Benchimol EI et al., 2015).

Appendix 4. Supplementary materials for chapter 4

Appendix 4-1. Read codes used to identify Parkinson's disease cases (diagnosis Read codes and symptom Read codes) and drug codes for antiparkinsonian medications**.**

Appendix 4-1a: Diagnosis Read codes used to identify cases of Parkinson's disease.

Medcode	Parkinson's disease diagnosis Read code description
Eu02300	[X]Dementia in Parkinson's disease
F11x900	Cerebral degeneration in Parkinson's disease
F12..00	Parkinson's disease
F12z.00	Parkinson's disease NOS
F130300	Parkinsonism with orthostatic hypotension

Appendix 4-1b: Parkinson's disease symptom Read codes and Read codes for Parkinsonism.

Medcode	Parkinson's disease symptom Read code description
2944.00	O/E - muscle rigid - cogwheel
2944.11	O/E - cog wheel rigidity
297A.00	O/E - Parkinsonian tremor
2987.00	O/E -Parkinson flexion posture
2987.11	O/E - Parkinson posture
2994.00	O/E-festination-Parkinson gait
2994.11	O/E - Parkinson gait
A94y100	Syphilitic parkinsonism
F123.00	Postencephalitic parkinsonism
F12X.00	Secondary parkinsonism, unspecified
F13z300	Akinetic rigid syndrome
Fyu2100	[X]Other secondary parkinsonism
Fyu2200	[X]Parkinsonism in diseases classified elsewhere
Fyu2900	[X]Secondary parkinsonism, unspecified

Appendix 4-1c: Antiparkinsonian medications and their corresponding Read codes in THIN.

Drugcode	Medication
50951978	Ropinirole 6mg modified-release tablets
50952978	Ropinirole 6mg modified-release tablets
50953978	Ropinirole 3mg modified-release tablets
50954978	Ropinirole 3mg modified-release tablets
51009978	Ropinirole 8mg modified-release tablets
51010978	Ropinirole 4mg modified-release tablets
51011978	Ropinirole 2mg modified-release tablets
51481978	Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets

51489978	Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets
51490978	Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets
51500978	Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets
51858978	Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets
51859978	Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets
51860978	Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets
52615979	Entacapone 200mg tablets tablets
55925979	Ropinirole 8mg modified-release tablets
55926979	Ropinirole 4mg modified-release tablets
55927979	Ropinirole 2mg modified-release tablets
57019978	Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets
57039978	Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets
57040978	Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg
57045978	Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets
59211978	Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets
59212978	Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets
59213978	Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets
60783979	Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets
60784979	Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets
61163979	Ropinirole 250microgram tablets
62159979	Apomorphine 100mg/20ml solution for infusion pre-filled syringes
63652979	Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets
63654979	Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets
64893979	Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets
64901979	Ropinirole 8mg modified-release tablets
64907979	Ropinirole 4mg modified-release tablets
64912979	Ropinirole 4mg modified-release tablets
64913979	Ropinirole 2mg modified-release tablets
64914979	Ropinirole 2mg modified-release tablets
72063979	Rotigotine 8mg/24hours transdermal patches
80178979	Entacapone 200mg/5ml oral suspension
80430979	Co-careldopa 6.25mg/25mg/5ml oral suspension
80436979	Co-careldopa 2.5mg/10mg/5ml oral suspension
80438979	Co-careldopa 12.5mg/50mg/5ml oral suspension
80939998	Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets
81142998	Ropinirole 8mg modified-release tablets
81143998	Ropinirole 4mg modified-release tablets
81144998	Ropinirole 2mg modified-release tablets
82380998	Co-careldopa 25mg/100mg tablets
82381998	Co-careldopa 12.5mg/50mg tablets
82382998	Co-careldopa 25mg/250mg tablets
82383998	Co-careldopa 10mg/100mg tablets
82384998	Co-careldopa 50mg/200mg modified-release tablets
82386998	Co-careldopa 25mg/100mg modified-release tablets
82651998	Co-careldopa 5mg/20mg/1ml intestinal gel 100ml cassette
82652998	Co-careldopa 5mg/20mg/1ml intestinal gel 100ml cassette
82774998	Rotigotine 3mg/24hours transdermal patches
82775998	Rotigotine 1mg/24hours transdermal patches
82776998	Rotigotine 3mg/24hours transdermal patches
82777998	Rotigotine 1mg/24hours transdermal patches

82863998	Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets
82864998	Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets
82865998	Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets
82866998	Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets
82937998	Bromocriptine 10mg capsules
82942998	Bromocriptine 5mg capsules
82943998	Bromocriptine 2.5mg tablets
82945998	Bromocriptine 1mg tablets
83201998	Co-careldopa 50mg/200mg modified-release tablets
83202998	Co-careldopa 25mg/100mg modified-release tablets
83777998	Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets
83778998	Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets
83882998	Ropinirole 8mg modified-release tablets
83883998	Ropinirole 4mg modified-release tablets
83884998	Ropinirole 2mg modified-release tablets
83990998	Ropinirole 8mg modified-release tablets
83991998	Ropinirole 4mg modified-release tablets
83992998	Ropinirole 2mg modified-release tablets
84792979	Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets
84793979	Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets
84799979	Levodopa 150mg / carbidopa 37.5mg / entacapone 200mg tablets
84807979	Levodopa 100mg / carbidopa 25mg / entacapone 200mg tablets
84979998	Co-careldopa 50mg/200mg modified-release tablets
84980998	Co-careldopa 25mg/100mg modified-release tablets
85170998	Co-careldopa 5mg/20mg/1ml intestinal gel 100ml cassette
85362998	Apomorphine 50mg/5ml solution for injection ampoules
85363998	Apomorphine 30mg/3ml solution for injection pre-filled disposable devices
85364998	Apomorphine hydrochloride 20mg/2ml injection
85365998	Apomorphine 50mg/5ml solution for injection ampoules
85366998	Apomorphine 30mg/3ml solution for injection pre-filled disposable devices
85367998	Apomorphine 20mg/2ml solution for injection ampoules
85991998	Ropinirole 2mg tablets
85992998	Ropinirole 500microgram tablets
85993998	Ropinirole 500microgram tablets
85994998	Ropinirole 250microgram tablets
86120998	Co-careldopa 5mg/20mg/1ml intestinal gel 100ml cassette
86139998	Rotigotine transdermal patches
86140998	Rotigotine 8mg/24hours transdermal patches
86141998	Rotigotine 6mg/24hours transdermal patches
86142998	Rotigotine 4mg/24hours transdermal patches
86143998	Rotigotine 2mg/24hours transdermal patches
86144998	Rotigotine 2mg/24hr with 4mg/24hr with 6mg/24hr with 8mg/24hr patch
86145998	Rotigotine 8mg/24hours transdermal patches
86146998	Rotigotine 6mg/24hours transdermal patches
86147998	Rotigotine 4mg/24hours transdermal patches
86148998	Rotigotine 2mg/24hours transdermal patches
86828998	Rasagiline 1mg tablets
86829998	Rasagiline 1mg tablets
86932998	Tolcapone 100mg tablets
87055998	Apomorphine 50mg/10ml solution for infusion pre-filled syringes

87056998	Apomorphine 50mg/10ml solution for infusion pre-filled syringes
87389998	Co-careldopa 50mg/200mg modified-release tablets
87804998	Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets
87805998	Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets
87806998	Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets
87807998	Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets
87808998	Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets
87809998	Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets
88550998	Apomorphine 30mg/3ml solution for injection pre-filled disposable devices
88560997	Tolcapone 200mg tablets
88560998	Tolcapone 100mg tablets
88563997	Tolcapone fc 200mg tablet
88563998	Tolcapone 100mg tablets
88879998	Ropinirole 500micrograms with 1mg with 2mg tablet
88891998	Ropinirole 250mcg+500mcg+1mg tablets starter pack
88988996	Cabergoline 4mg tablets
88988997	Cabergoline 2mg tablets
88988998	Cabergoline 1mg tablets
88990996	Cabergoline 4mg tablets
88990997	Cabergoline 2mg tablets
88990998	Cabergoline 1mg tablets
89220998	Ropinirole 250micrograms with 500micrograms with 1mg tablet
89667998	Ropinirole 5mg tablets
89668996	Ropinirole 2mg tablets
89668997	Ropinirole 1mg tablets
89668998	Ropinirole 250microgram tablets
89669998	Ropinirole 5mg tablets
89670996	Ropinirole 2mg tablets
89670997	Ropinirole 1mg tablets
89670998	Ropinirole 250microgram tablets
89862979	Co-careldopa 25mg/100mg modified-release tablets
89920979	Co-careldopa 25mg/250mg tablets
89924979	Co-careldopa 25mg/250mg tablets
89925979	Co-careldopa 25mg/250mg tablets
89926979	Co-careldopa 25mg/250mg tablets
89933979	Co-careldopa 25mg/100mg tablets
89936979	Co-careldopa 25mg/100mg tablets
89937979	Co-careldopa 25mg/100mg tablets
89939979	Co-careldopa 25mg/100mg tablets
89940979	Co-careldopa 25mg/100mg tablets
89943979	Co-careldopa 10mg/100mg tablets
89944979	Co-careldopa 10mg/100mg tablets
89946979	Co-careldopa 10mg/100mg tablets
89948979	Co-careldopa 10mg/100mg tablets
89949979	Co-careldopa 10mg/100mg tablets
89953979	Co-careldopa 50mg/200mg modified-release tablets
89956979	Co-careldopa 50mg/200mg modified-release tablets
89957979	Co-careldopa 50mg/200mg modified-release tablets
90032997	Selegiline hydrochloride 10mg tablets
90032998	Selegiline hydrochloride 5mg tablets

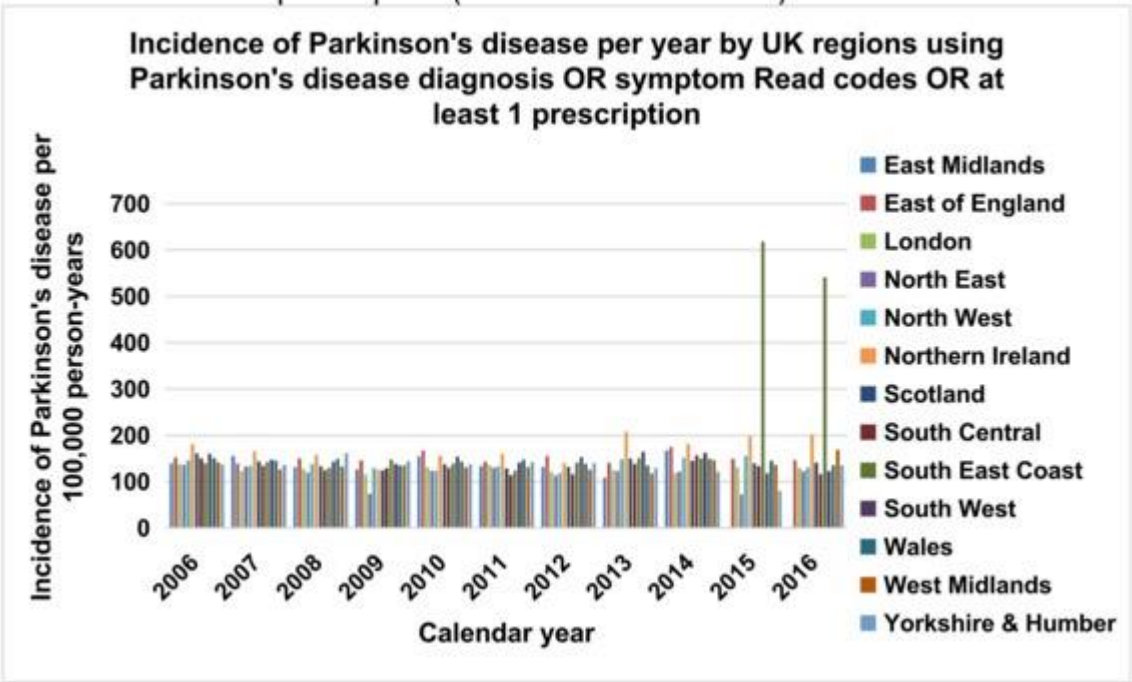
90565998	Ropinirole 500mcg+1mg+2mg tablets
90782997	Selegiline hydrochloride 10mg tablets
90782998	Selegiline hydrochloride 5mg tablets
91004997	Selegiline hydrochloride 10mg tablets
91004998	Selegiline hydrochloride 5mg tablets
91530998	Pergolide 50mcg+250mcg tablets starter pack
91760998	Pergolide 250microgram tablets and pergolide 50microgram tablets
91979998	Pergolide starter pack (pergolide 50 micrograms tablet with pergolide 250 micrograms tablet) 81 tablets
92202990	Co-careldopa 50mg/200mg modified-release tablets
92244997	Apomorphine hydrochloride 3mg sublingual tablets
92244998	Apomorphine hydrochloride 2mg sublingual tablets
92255990	Co-beneldopa 25mg/100mg capsules
92372990	Apomorphine 20mg/2ml solution for injection ampoules
92399990	Ropinirole 250microgram tablets
92509990	Ropinirole 1mg tablets
92534998	Pergolide 50mcg+250mcg tablets starter pack
92580990	Ropinirole 250microgram tablets
92603990	Ropinirole 2mg tablets
92798998	Cabergoline 500microgram tablets
92799998	Cabergoline 500microgram tablets
92914996	Apomorphine 3mg sublingual tablets sugar free
92914997	Apomorphine 2mg sublingual tablets sugar free
92914998	Apomorphine 50mg/5ml solution for injection ampoules
92915998	Apomorphine hydrochloride 30mg/3ml prefilled pen
92944979	Cabergoline 500microgram tablets
92947998	Co-careldopa 25mg/100mg modified-release tablets
93017990	Cabergoline 500microgram tablets
93220996	Co-careldopa 25mg/100mg modified-release tablets
93220997	Co-careldopa 50mg/200mg modified-release tablets
93220998	Co-careldopa 12.5mg/50mg tablets
93221996	Co-careldopa 25mg/100mg tablets
93221997	Co-careldopa 25mg/100mg tablets
93221998	Co-careldopa 10mg/100mg tablets
93222996	Co-beneldopa 25mg/100mg modified-release capsules
93222997	Co-beneldopa 25mg/100mg dispersible tablets sugar free
93222998	Co-beneldopa 12.5mg/50mg dispersible tablets sugar free
93223996	Co-beneldopa 50mg/200mg capsules
93223997	Co-beneldopa 25mg/100mg capsules
93223998	Co-beneldopa 12.5mg/50mg capsules
93991990	Co-careldopa 25mg/100mg tablets
93993990	Co-careldopa 10mg/100mg tablets
94414998	Co-beneldopa 25mg/100mg modified-release capsules
94415998	Co-beneldopa 25mg/100mg modified-release capsules
94416998	Co-beneldopa 25mg/100mg modified-release capsules
94448996	Co-careldopa 25mg/100mg modified-release tablets
94448997	Co-careldopa 50mg/200mg modified-release tablets
94448998	Co-careldopa 12.5mg/50mg tablets
94450996	Co-careldopa 25mg/100mg modified-release tablets
94450997	Co-careldopa 50mg/200mg modified-release tablets

94450998	Co-careldopa 12.5mg/50mg tablets
94761979	Ropinirole 1mg tablets
94786979	Pergolide 250microgram tablets
94824979	Co-beneldopa 25mg/100mg capsules
94957998	Co-careldopa 50mg/200mg modified-release tablets
95069997	Co-beneldopa 50mg/200mg capsules
95069998	Co-beneldopa 25mg/100mg dispersible tablets sugar free
95070996	Co-beneldopa 25mg/100mg capsules
95070997	Co-beneldopa 12.5mg/50mg dispersible tablets sugar free
95070998	Co-beneldopa 12.5mg/50mg capsules
95941998	Bromocriptine 10mg capsules
95942996	Bromocriptine 5mg capsules
95942997	Bromocriptine 2.5mg tablets
95942998	Bromocriptine 1mg tablets
96020996	Co-careldopa 25mg/100mg tablets
96020997	Co-careldopa 25mg/100mg tablets
96020998	Co-careldopa 10mg/100mg tablets
96021997	Co-beneldopa 25mg/100mg dispersible tablets sugar free
96021998	Co-beneldopa 12.5mg/50mg dispersible tablets sugar free
96022996	Co-beneldopa 50mg/200mg capsules
96022997	Co-beneldopa 25mg/100mg capsules
96022998	Co-beneldopa 12.5mg/50mg capsules
96023998	Levodopa 500mg tablets
96024996	Levodopa 500mg capsule
96024997	Levodopa 250mg capsule
96024998	Levodopa 125mg capsule
96313992	Levodopa/benserazide 40 mg cap
96314992	Levodopa 40 mg cap
96818990	Bromocriptine 2.5mg tablets
96872996	Co-careldopa 25mg/100mg tablets
96872997	Co-careldopa 25mg/100mg tablets
96872998	Co-careldopa 10mg/100mg tablets
96928992	Co-beneldopa 12.5mg/50mg capsules
96953998	Amantadine 100mg capsules
97033988	Co-careldopa 25mg/100mg tablets
97033989	Co-careldopa 25mg/100mg tablets
97033990	Co-careldopa 10mg/100mg tablets
97049997	Co-beneldopa 50mg/200mg capsules
97049998	Co-beneldopa 25mg/100mg dispersible tablets sugar free
97050996	Co-beneldopa 25mg/100mg capsules
97050997	Co-beneldopa 12.5mg/50mg dispersible tablets sugar free
97050998	Co-beneldopa 12.5mg/50mg capsules
97554998	Entacapone 200mg tablets
97580998	Amantadine 50mg/5ml oral solution sugar free
97657992	Levodopa 40 mg tab
97781990	Bromocriptine 2.5mg tablets
98056996	Pergolide 1mg tablets
98056997	Pergolide 250microgram tablets
98056998	Pergolide 50microgram tablets
98325998	Entacapone 200mg tablets

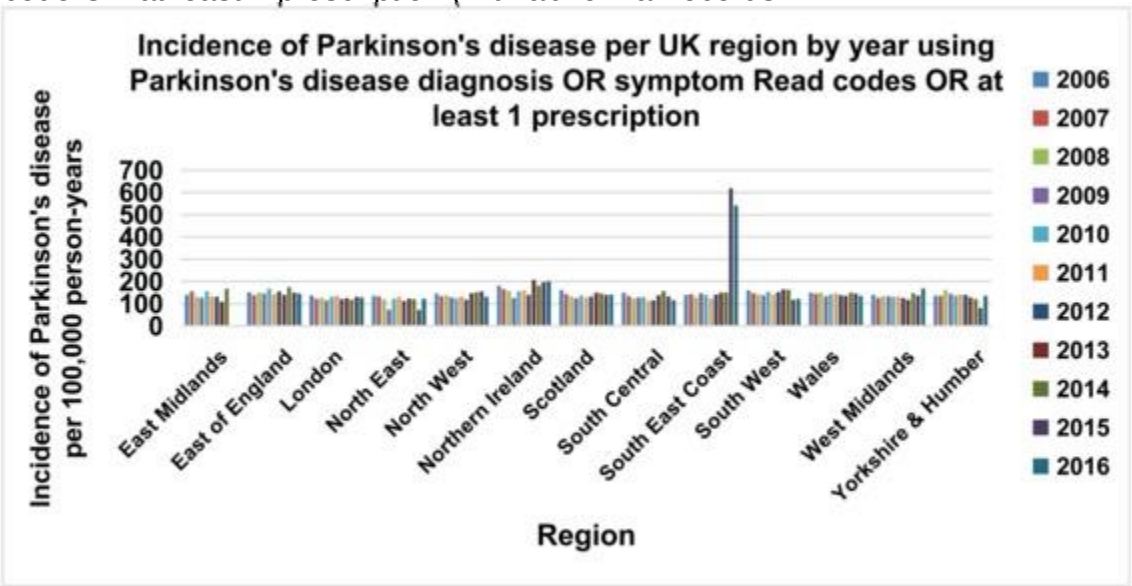
98337990	Bromocriptine 2.5mg tablets
98401998	Co-careldopa 25mg/100mg tablets
98402998	Co-careldopa 25mg/250mg tablets
98688998	Amantadine 50mg/5ml oral solution sugar free
98933996	Pergolide 1mg tablets
98933997	Pergolide 250microgram tablets
98933998	Pergolide 50microgram tablets
99088998	Amantadine 100mg capsules
99139998	Co-careldopa 10mg/100mg tablets
99282998	Bromocriptine 10mg capsules
99283996	Bromocriptine 5mg capsules
99283997	Bromocriptine 2.5mg tablets
99283998	Bromocriptine 1mg tablets
99495998	Levodopa 500mg tablets
99635998	Amantadine 100mg capsules
99772990	Bromocriptine 2.5mg tablets
99774990	Bromocriptine 2.5mg tablets
99874996	Levodopa 500mg capsules
99874997	Levodopa 250mg capsules
99874998	Levodopa 125mg capsules
99938992	Co-beneldopa 25mg/100mg capsules
99939992	Levodopa 125 mg tab

Appendix 4-2: Additional graphs from section 4.5: Identification and reducing sources of misclassification bias in the identification of Parkinson's disease cases.

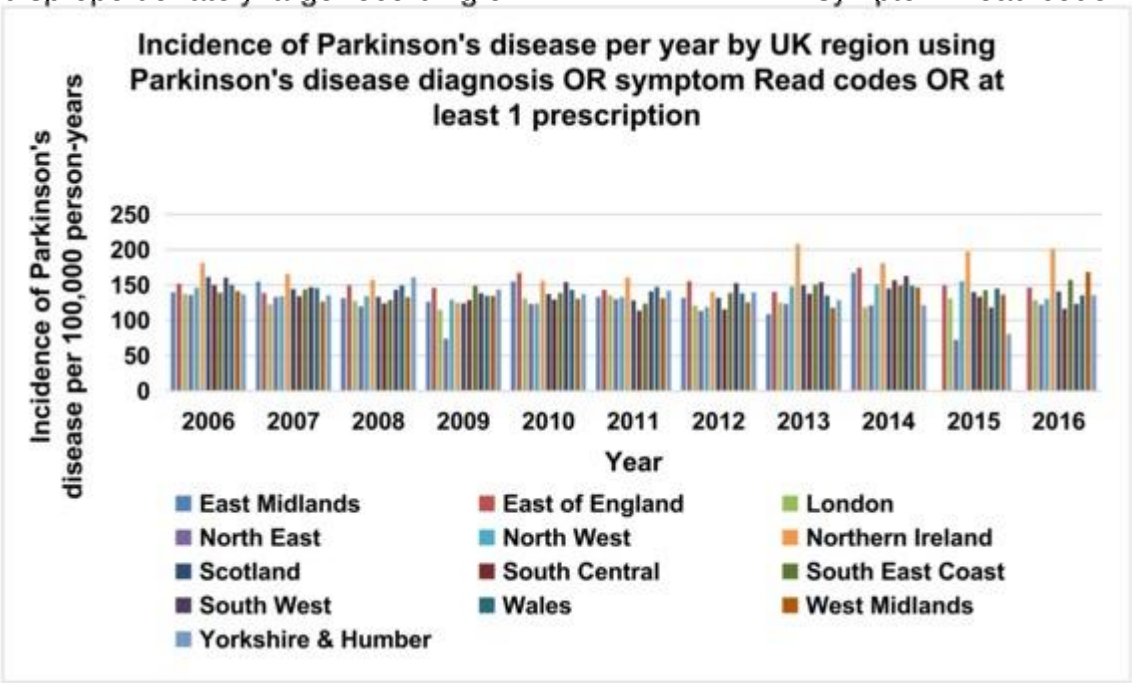
Appendix 4-2a: Figure 4-1: Graph showing incidence of Parkinson's disease per year by UK region using Parkinson's disease diagnosis OR symptom Read code OR at least 1 prescription (with abnormal records).



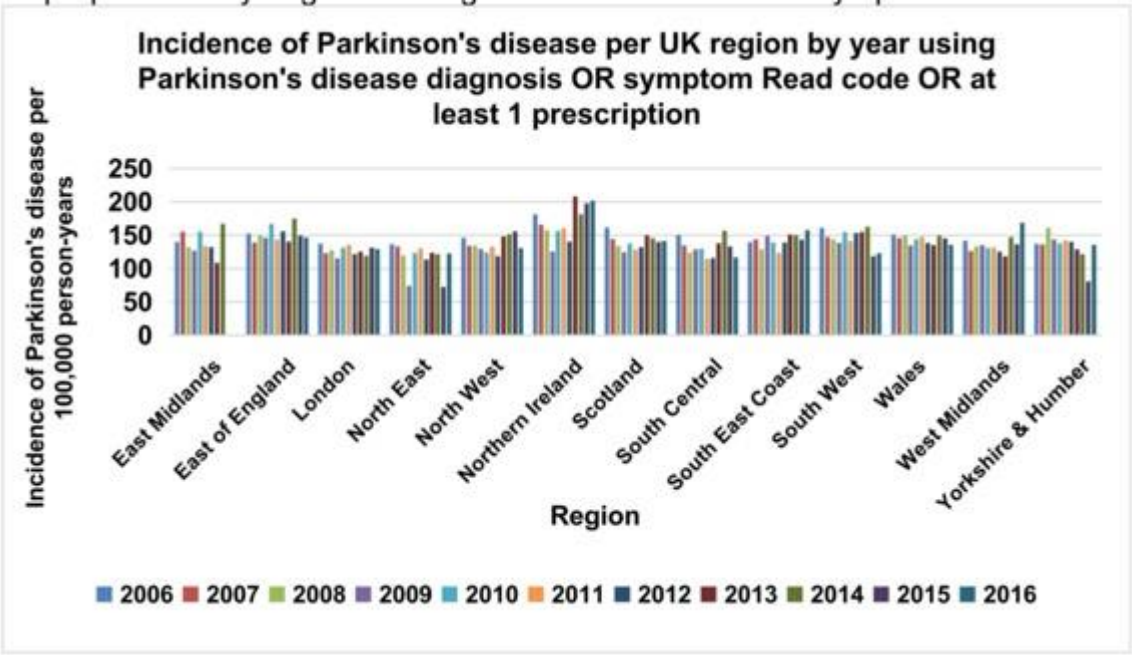
Appendix 4-2a: Figure 4-2: Graph showing incidence of Parkinson's disease per year by UK region using Parkinson's disease diagnosis OR symptom Read code OR at least 1 prescription (with abnormal records



Appendix 4-2b: Figure 4-3: Graph showing incidence of Parkinson's disease per year by UK region using Parkinson's disease diagnosis OR symptom Read code OR at least 1 prescription after excluding the practice with disproportionately large recording of Parkinson's disease symptom Read code.



Appendix 4-2b Figure 4-4: Graph showing incidence of Parkinson's disease per UK region by year using Parkinson's disease diagnosis OR symptom Read code OR at least 1 prescription after excluding the practice with disproportionately large recording of Parkinson's disease symptom Read code.

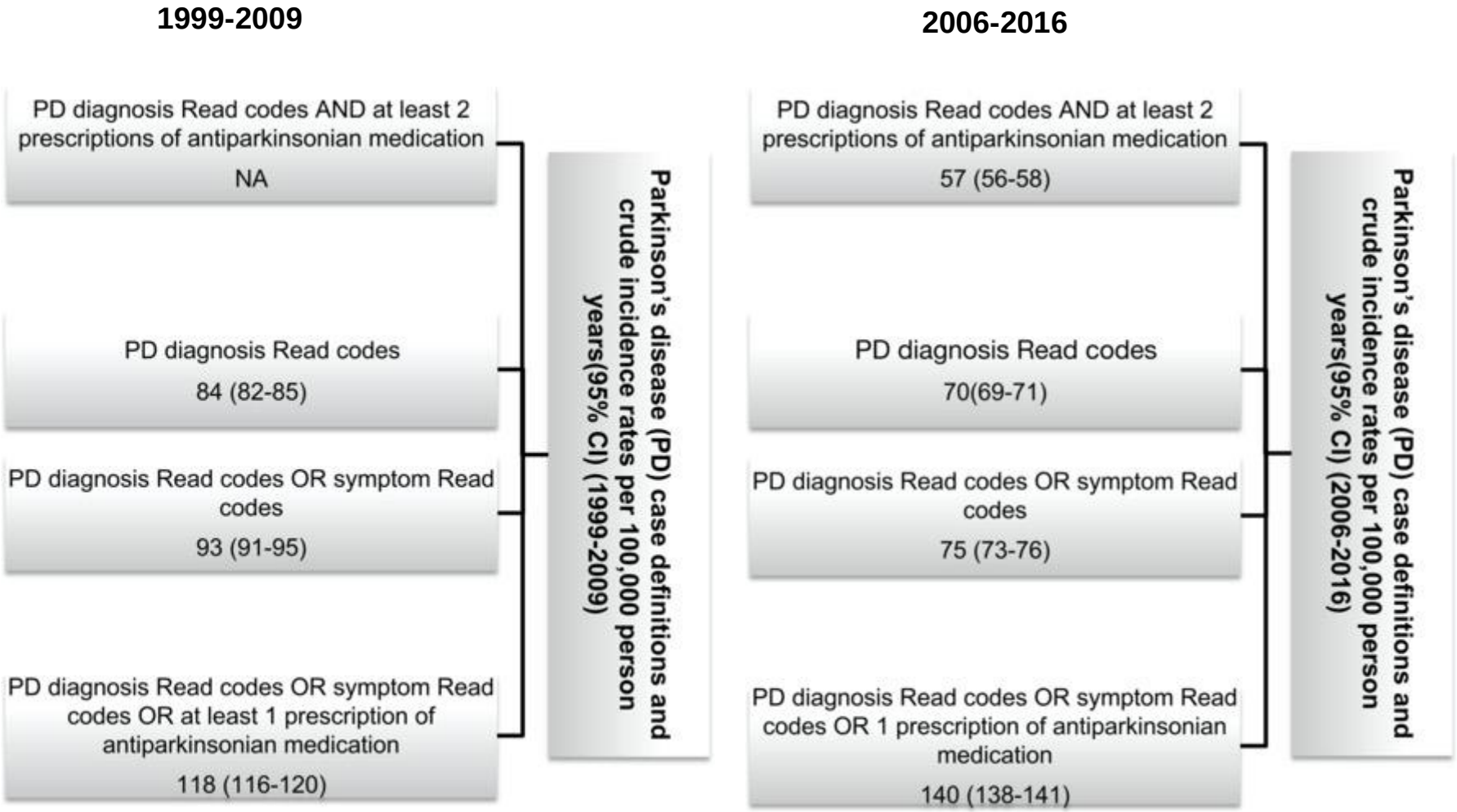


Appendix 4-3: Exploratory work to ascertain incidence of Parkinson's disease in THIN between 2006 and 2016.

1. I compared incidence rates in this study to the results of a previous study in THIN using the same case definitions, including for the previous study's time period **(Appendix 4-3a).** Data was extracted from 1999-2006 shown in **Appendix 4-3b**.

2. I also compared incidence (per 100,000) of PD by age-group (2011-2015) in THIN and CPRD using similar Read codes (diagnostic Read codes: F12..00 Parkinson's disease, F120.00 Paralysis agitans and F12z.00 Parkinson's disease not otherwise specified). These were comparable as shown in **Appendix 4-3c.** This showed similar results.

Appendix 4-3a: Comparing incidence rates of Parkinson's disease with previous study in THIN



Appendix 4-3b: Incidence rates (per 100,000 per years) of PD (using different case definitions) comparing previous study in THIN.

Case definition (same code list)	**Overall crude incidence per 100,000 person-years (95% Confidence Interval) (1999-2006)** (Results from Previous study)	**Overall crude incidence per 100,000 person-years (95% Confidence Interval) (1999-2006)** (Results of this study conducted using previous time period in the present)	**Overall crude incidence per 100,000 person-years (95% Confidence Interval) (2006-2016)** (Results of present study)
Parkinson's disease diagnosis Read codes AND at least 2 prescriptions of antiparkinsonian medication	NA	NA	57 (56-58)
Parkinson's disease diagnosis Read codes	84 (82-85)	84 (82-85)	70 (69-71)
Parkinson's disease diagnosis OR symptom Read codes	93 (91-95)	90 (88-91)	75(73-76)
Parkinson's disease diagnosis Read code OR symptom Read code OR at least 1 prescription of antiparkinsonian medication	118 (116-120)	113 (111-115)	140 (138-141)

Appendix 4-3c: Comparing incidence rates (per 100,000 PYAR) of Parkinson's disease by age-group (2011-2015) with results of the Parkinson's UK study using similar case definitions (diagnostic Read codes).

THIN

Gender	Age	N	Person years	Incidence Rate per 100,000	95% CI lower	95% CI Upper
All	50-54	335	33.9	9.9	8.9	11.0
All	55-59	581	30.9	18.8	17.3	20.3
All	60-64	1057	29.4	35.9	33.8	38.2
All	65-69	1662	25.3	65.7	62.7	69.0
All	70-74	2303	20.1	114.6	110.0	119.3
All	75-79	2731	16.2	168.6	162.4	175.1
All	80-84	2170	11.8	183.2	175.6	191.1
All	85-89	1228	7.1	172.7	163.3	182.6
All	90-94	337	2.9	116.5	104.7	129.6
All	95-99	41	0.8	50.4	37.1	68.5

CI Confidence Interval

CPRD

Gender	Age	N	Person years	Incidence Rate per 100,000	95% CI lower	95% CI Upper
All	50-54	134	15.8	9.1	7.6	10.7
All	55-59	232	14.8	18.2	15.9	20.7
All	60-64	398	11.9	33.5	30.3	37.0
All	65-69	714	11.5	62.3	57.8	67.1
All	70-74	969	8.5	113.4	106.3	120.7
All	75-79	1207	7.1	173.5	163.9	183.6
All	80-84	1032	5.3	195.5	183.7	207.8
All	85-89	615	3.3	186.3	171.9	207.1
All	90-94	179	1.5	115.1	98.9	133.3
All	95-99	NA	NA	NA	NA	NA

Appendices 4-4 to 4-13: Supplementary tables and figures from PD incidence study.

Appendix 4-4: Table 4-3: Incidence of Parkinson's disease by sociodemographic factors, calendar year and region using diagnosis Read codes. *IRR adjusted for age, gender, year, Townsend score and region.

	Number of cases	Person-years (100,000)	Incidence of PD Rate per 100,000 (95% CI)	Adjusted *IRR (95% CI)
Overall	12,336		70 (69-71)	
Age band, years				
50-54	330	33.60	9.82 (8.81-10.94)	(Reference)
55-59	573	30.68	18.67 (17.21-20.27)	1.89 (1.64-2.17)
60-64	1,043	29.14	35.79 (33.68-38.01)	3.69 (3.24-4.19)
65-69	1,653	25.01	66.09 (63.98-69.35)	6.77 (5.98-7.65)
70-74	2,286	19.89	114.92 (110.31-119.73)	11.94 (10.59-13.46)
75-80	2,704	16.03	168.64 (162.41-175.12)	17.77 (15.78-20.01)
80-84	2,158	11.73	183.95 (176.35-191.88)	19.74 (17.49-22.27)
85-89	1,214	7.05	172.39 (162.97-182.36)	18.97 (16.70-21.53)
90-94	334	2.87	116.42 (104.58-129.60)	13.24 (11.30-15.52)
95+	41	0.81	50.83 (37.42-69.03)	5.85 (4.16-8.24)
Sex				
Male	7,423	83.80	88.58 (86.59-90.62)	(Reference)
Female	4,913	93.01	52.83 (51.38-54.33)	0.53 (0.51-0.55)
Townsend quintile				
1	3,349	83.80	73.84 (71.38-76.38)	(Reference)
2	2,837	93.01	71.19 (68.62-73.85)	0.93 (0.89-0.98)
3	2,309	83.80	67.52 (64.82-70.33)	0.89 (0.84-0.94)
4	1,801	93.01	66.42 (63.4-69.56)	0.87 (0.82-0.92)
5 (Most deprived)	1,127	83.80	65.26 (61.56-69.19)	0.86 (0.81-0.93)
Missing	913	93.01	70.15 (65.75-74.85)	
Year				
2006	1,174	15.90	73.90 (69.79-78.24)	(Reference)
2007	1193	16.46	72.46 (68.46-76.69)	0.97 (0.90-1.06)
2008	1,253	16.88	74.22 (70.23-78.45)	1.00 (0.92-1.09)
2009	1227	17.09	71.80 (67.89-75.93)	0.94 (0.87-1.02)
2010	1132	16.86	67.14 (63.34-71.17)	0.88 (0.81-0.96)
2011	1137	17.19	66.14 (62.41-70.10)	0.88 (0.81-0.95)
2012	1212	17.42	69.56 (65.75-73.59)	0.91 (0.84-0.99)
2013	1164	17.01	68.42 (64.60-72.47)	0.89 (0.82-0.97)
2014	1146	16.18	70.81 (66.83-75.03)	0.93 (0.85-1.01)
2015	910	14.05	64.77 (60.70-69.12)	0.84 (0.77-0.92)
2016	788	11.75	67.00 (62.49-71.85)	0.85 (0.77-0.94)
Region				
Wales	1225	20.02	61.20 (57.80-64.70)	(Reference)
East Midlands	249	3.64	68.30 (60.30-77.30)	1.08 (0.91-1.28)
East of England	755	9.60	78.70(73.30-84.50)	1.25 (1.11-1.42)
London	1225	17.15	71.40 (67.50-75.60)	1.23 (1.11-1.36)
North East	258	3.63	71.40 (63.20-80.60)	1.19 (1.00-1.42)
North West	1124	16.88	66.60 (62.80-70.60)	1.10 (0.99-1.23)
Northern Ireland	587	7.24	81.00 (74.70-87.90)	1.42 (1.25-1.61)
Scotland	1893	28.94	65.40 (62.50-68.40)	1.16 (1.06-1.27)
South Central	1373	18.83	72.90 (69.20-76.90)	1.16 (1.04-1.28)
South East Coast	1414	18.58	76.10 (72.20-80.20)	1.22 (1.10-1.35)
South West	1069	14.63	73.00 (68.80-77.60)	1.12 (1.01-1.25)
West Midlands	936	14.2	65.40 (61.30-69.70)	1.05 (0.94-1.18)
Yorkshire & Humber	228	3.3	67.90 (59.60-77.30)	1.12 (0.94-1.35)

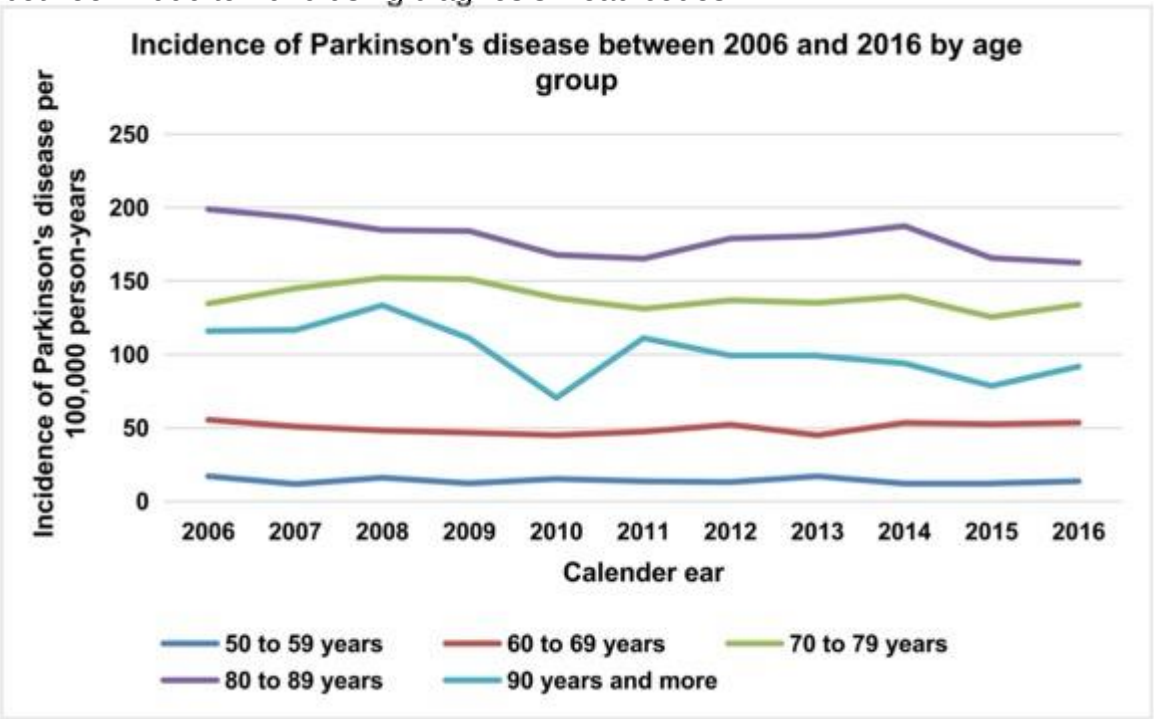
***IRR adjusted for age, gender, calendar year, social deprivation and region. CI-Confidence interval

Appendix 4-5: Table 4-4 Incidence of Parkinson's disease by sociodemographic factors, calendar year and region using diagnosis OR symptom Read codes. *IRR adjusted for age, gender, year, Townsend score and region.

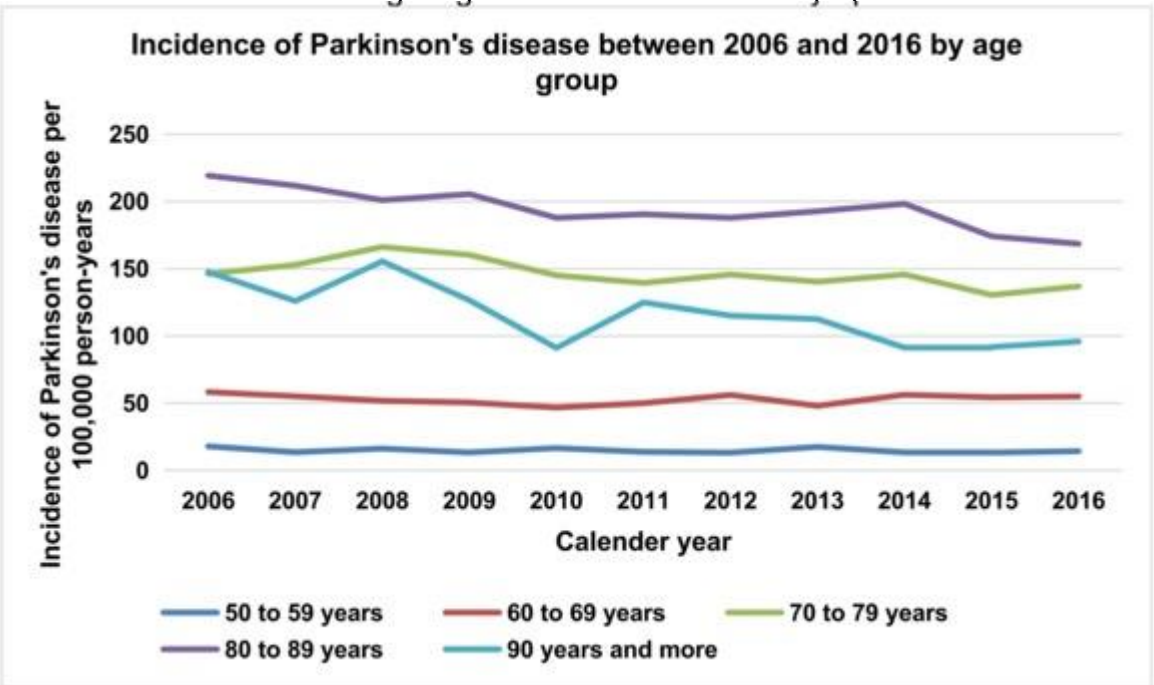
	Number of cases	Person-years (100,000)	Incidence of PD Rate per 100,000 (95% CI)	Adjusted *IRR (95% CI)
Overall	13173		75(73-76)	
Age, years				
50-54	353	33.60	10.51 (9.47-11.66)	(Reference)
55-59	604	30.68	19.69 (18.18-21.32)	1.87 (1.63-2.14)
60-64	1101	29.14	37.79 (35.62-40.09)	3.65 (3.23-4.14)
65-69	1755	25.0	70.19 (66.98-73.55)	6.78 (6.03-7.65)
70-74	2417	19.88	121.57 (116.82-126.52)	11.88 (10.58-13.35)
75-79	2853	16.02	178.07 (171.65-184.73)	17.64 (15.72-19.80)
80-84	2336	11.72	199.34 (191.42-207.59)	20.17 (17.95-22.67)
85-89	1327	7.04	188.54 (178.66-198.96)	19.47 (17.23-22.02)
90-94	375	2.86	130.90 (118.30-144.84)	14.13 (12.14-16.44)
95+	52	0.81	64.52 (49.17-84.67)	7.01 (5.16-9.52)
Sex				
Male	7908	83.76	94.41 (92.35-96.51)	(Reference)
Female	5265	92.98	56.63 (55.12-58.18)	0.53 (0.51-0.55)
Townsend quintile				
1	3548	45.34	78.25 (75.72-80.87)	(Reference)
2	2994	39.84	75.16 (72.51-77.90)	0.93 (0.88-0.98)
3	2473	34.19	72.32 (69.53-75.22)	0.90 (0.85-0.94)
4	1949	27.10	71.91 (68.79-75.18)	0.88 (0.83-0.94)
5 (Most deprived)	1232	17.26	71.39 (67.51-75.49)	0.89 (0.83-0.95)
Missing	977	13.01	75.09 (70.53-79.95)	
Year				
2006	1274	15.89	80.16 (75.87-84.68)	(Reference)
2007	1286	16.46	78.14 (73.99-82.53)	0.97 (0.89-1.05)
2008	1357	16.87	80.42 (76.26-84.82)	1.00 (0.93-1.09)
2009	1329	17.08	77.81 (73.73-82.10)	0.94 (0.87-1.02)
2010	1214	16.85	72.09 (68.1-76.20)	0.88 (0.81-0.95)
2011	1231	17.18	71.64 (67.75-75.75)	0.88 (0.81-0.95)
2012	1286	17.42	73.84 (69.91-77.98)	0.90 (0.83-0.97)
2013	1226	17.01	72.09 (68.17-76.24)	0.86 (0.80-0.94)
2014	1205	16.18	74.49 (70.39-78.81)	0.90 (0.83-0.98)
2015	954	14.04	67.93 (63.79-72.38)	0.81 (0.74-0.89)
2016	811	11.76	68.98 (64.39-73.89)	0.81 (0.74-0.89)
Region				
Wales	1305	20.0	65.20 (61.76-68.83)	(Reference)
East Midlands	271	3.60	74.33 (65.99-83.73)	1.09 (0.92-1.29)
East of England	820	10.0	85.50 (79.85-91.56)	1.27 (1.13-1.43)
London	1310	17.1	76.43 (72.40-80.68)	1.23 (1.11-1.36)
North East	275	3.60	76.09 (67.60-85.63)	1.19 (1.00-1.42)
North West	1216	16.9	72.08 (68.14-76.25)	1.12 (0.99-1.24)
Northern Ireland	612	7.20	84.64 (78.20-91.61)	1.39 (1.22-1.58)
Scotland	2021	28.9	69.86 (66.88-72.98)	1.16 (1.06-1.27)
South Central	1475	18.8	78.34 (74.46-82.46)	1.17 (1.05-1.29)
South East Coast	1488	18.6	80.12 (76.15-84.30)	1.20 (1.08-1.33)
South West	1149	14.6	78.55 (74.13-83.22)	1.13 (1.02-1.26)
West Midlands	980	14.3	68.48 (64.32-72.89)	1.04 (0.93-1.16)
Yorkshire & Humber	250	3.40	74.45 (65.76-84.27)	1.14 (0.95-1.36)

***IRR adjusted for age, gender, calendar year, social deprivation and region. CI-Confidence interval

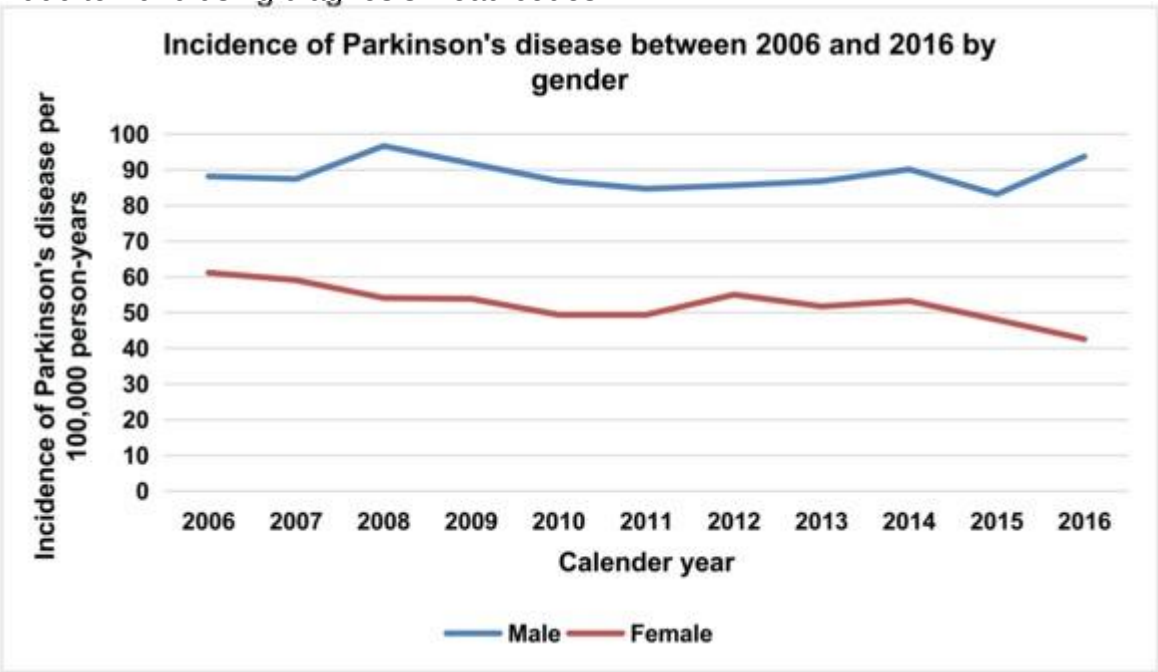
Appendix 4-6: Incidence of Parkinson's disease in THIN by age group between 2006 to 2016 using diagnosis Read codes.



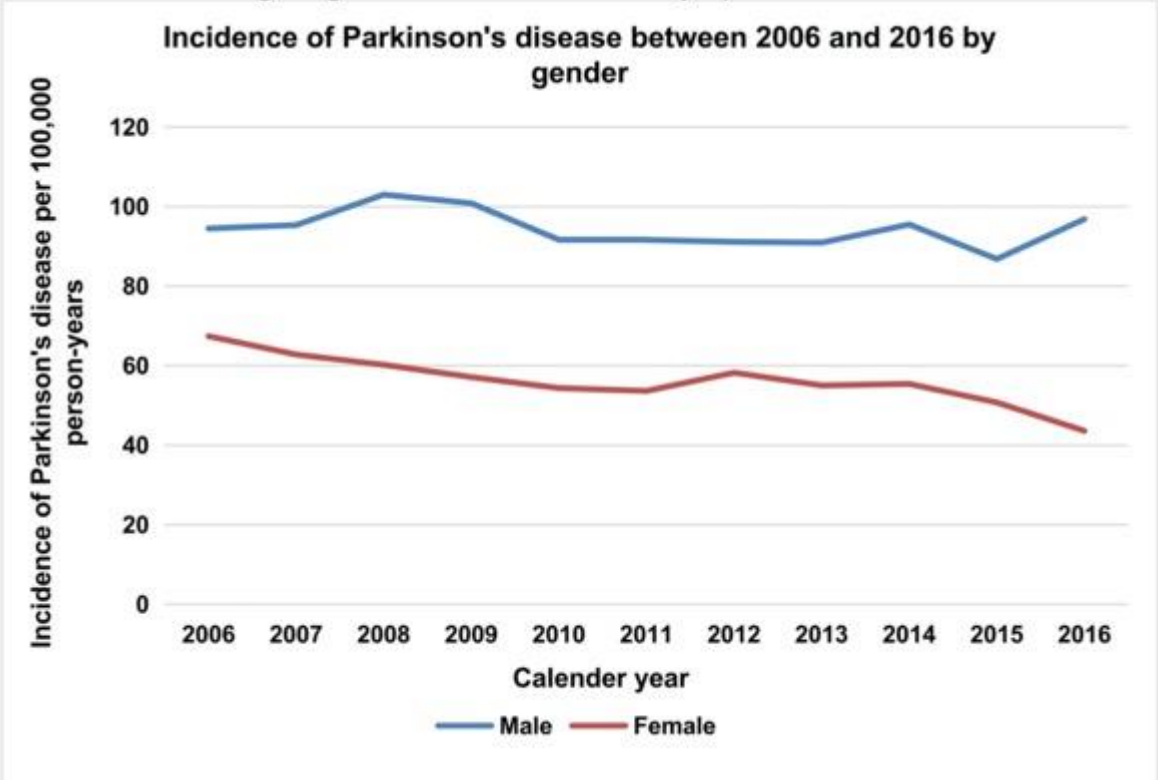
Appendix 4-7: Incidence of Parkinson's disease in THIN by age group between 2006 to 2016 using diagnosis Read codes OR symptom Read codes.



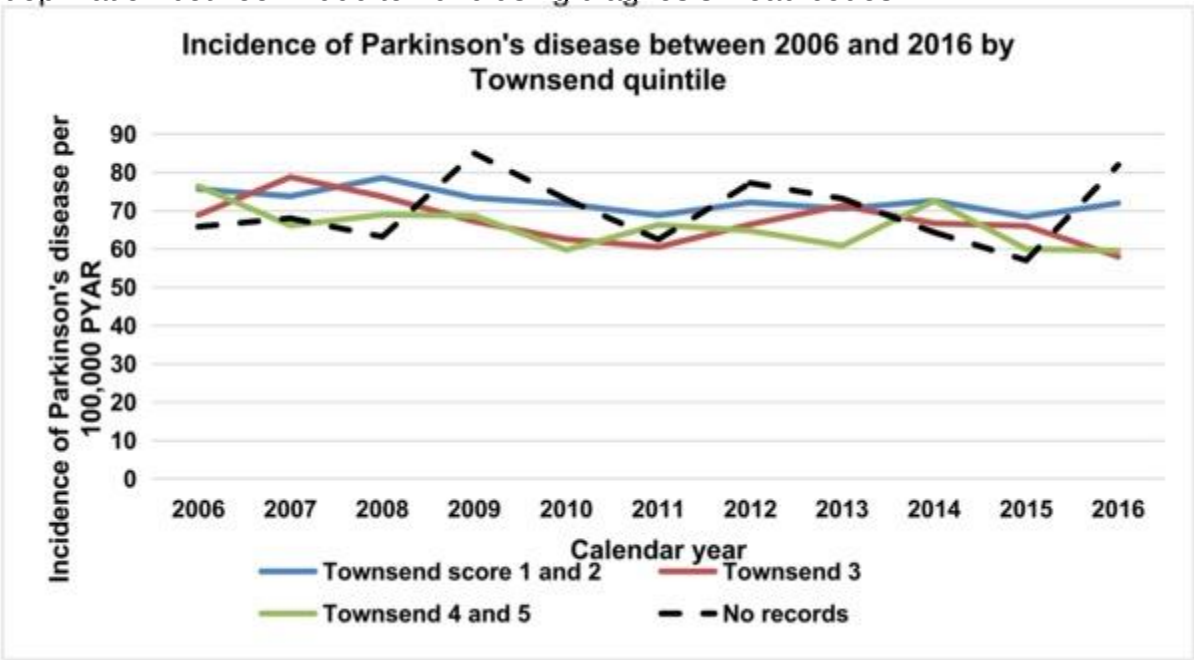
Appendix 4-8: Incidence of Parkinson's disease in THIN by gender between 2006 to 2016 using diagnosis Read codes



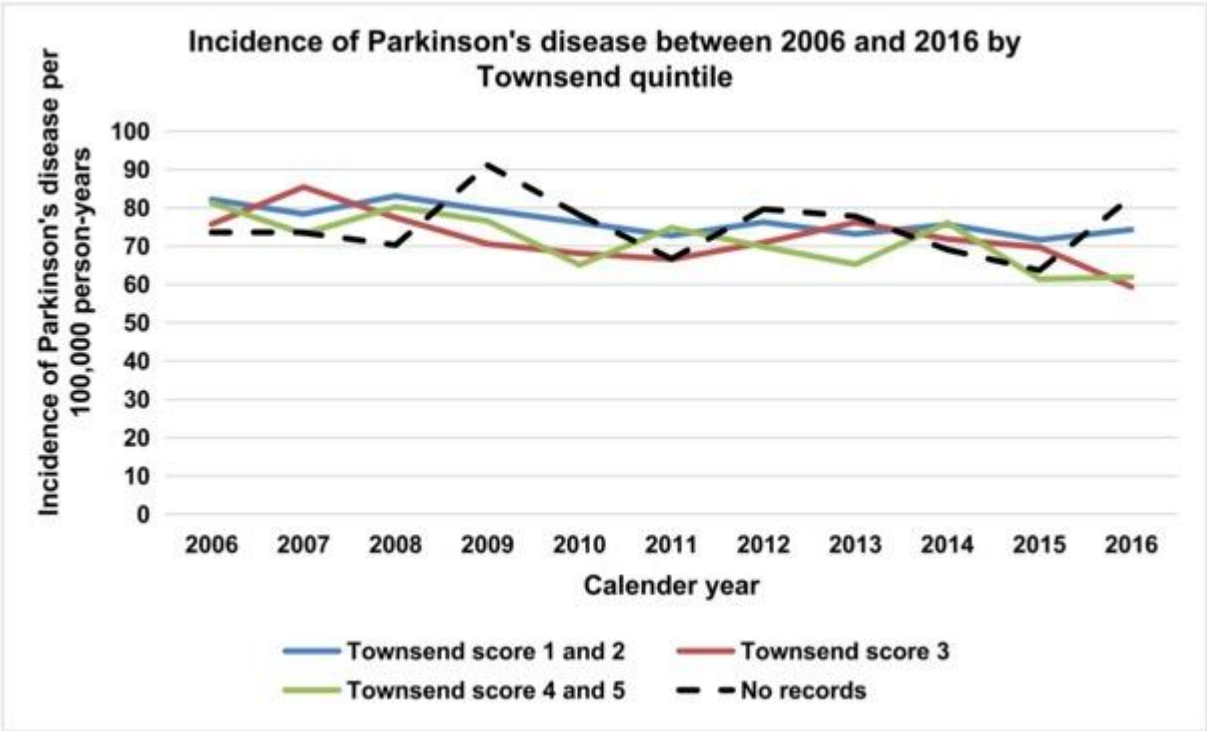
Appendix 4-9: Incidence of Parkinson's disease in THIN by gender between 2006 to 2016 using diagnosis Read codes OR symptom Read codes.



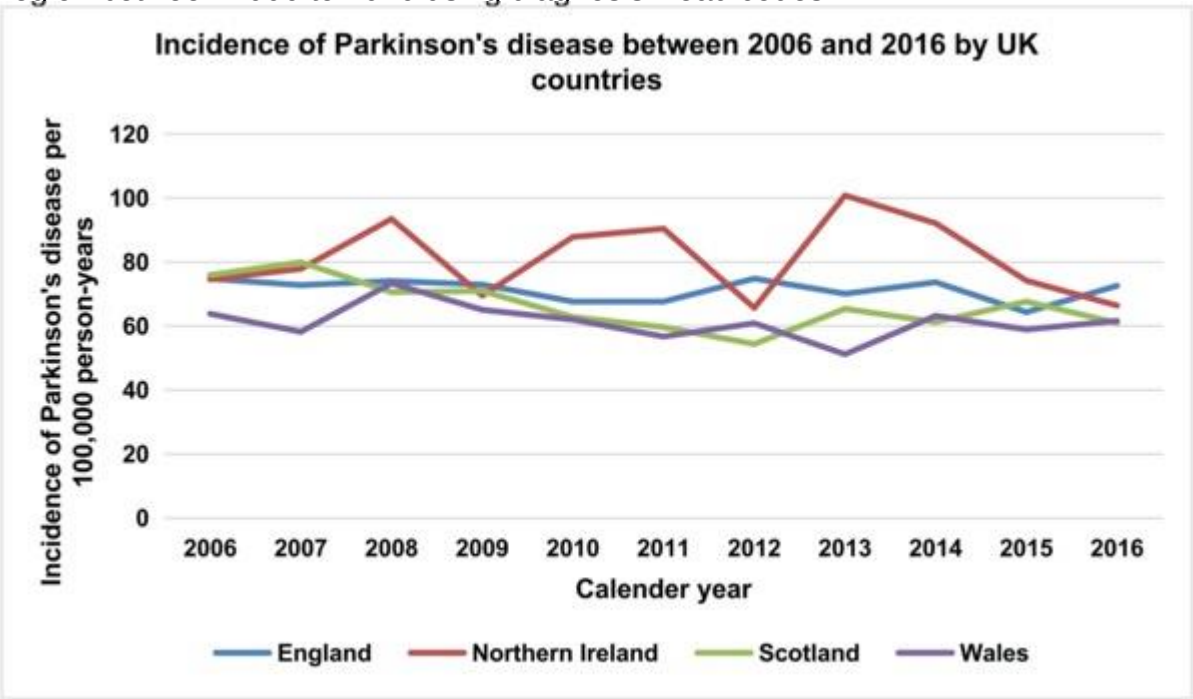
Appendix 4-10: Incidence of Parkinson's disease in THIN by degree of social deprivation between 2006 to 2016 using diagnosis Read codes



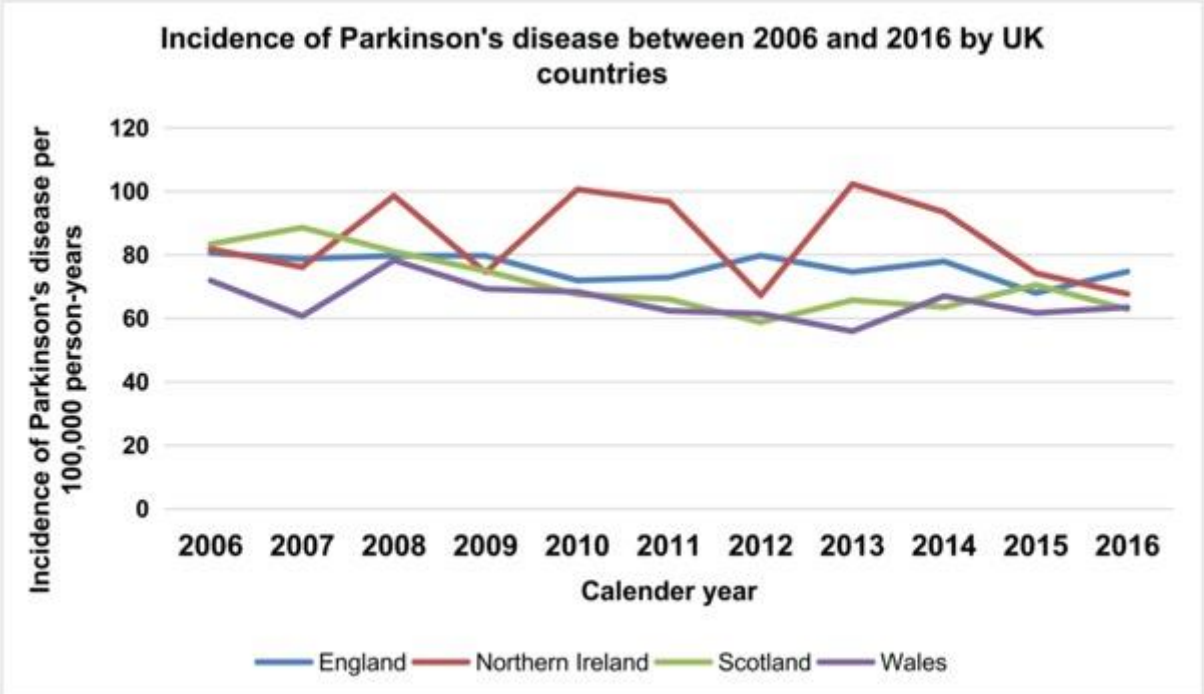
Appendix 4-11: Incidence of Parkinson's disease in THIN by degree of social deprivation between 2006 to 2016 using diagnosis Read code OR symptom Read codes.



Appendix 4-12: Incidence of Parkinson's disease in THIN by geographical region between 2006 to 2016 using diagnosis Read codes.



Appendix 4-13: Incidence of Parkinson's disease in THIN by geographical region between 2006 to 2016 using diagnosis Read code OR symptom Read codes.



Appendix 5. Supplementary materials for chapter 5

Appendix 5-1: Manuscript (published online on the 5th of August 2021) based on work done in chapter 5 of this thesis.

Check for updates

RESEARCH ARTICLE

Mortality of People with Parkinson's Disease in a Large UK-Based Cohort Study: Time Trends and Relationship to Disease Duration

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ABSTRACT: Background: Parkinson's disease (PD) is associated with increased mortality, but little is known about changes over time, and relationship to disease progression. **Objectives:** To explore how PD mortality rates have changed over time and their relationship to disease duration and demographics using a large population-based cohort in the UK. **Methods:** We included individuals aged 50+ years with a first recording of PD diagnosis and at least two prescriptions of any antiparkinsonian drug actively registered within a general practice from 2006 to 2016 and up to six frequency-matched controls from The Health Improvement Network (THIN) database. We estimated adjusted mortality rates using multivariable Poisson regression. **Results:** A total of 10,104 people with a diagnosis of PD and 55,664 people without PD were included. Overall, PD was associated with slightly increased mortality compared to non-PD controls (adjusted mortality rate ratio: 1.14; 95% CI: 1.03 to 1.19). Adjusted mortality rates per 1000 person-years at risk for people with PD approximately doubled in the 5 years following diagnosis from 43 (95% CI: 38 to 48) to 75 (95% CI: 64 to 85). Following adjustments for age, gender, and time since diagnosis, mortality rates between 2007 and 2016 declined more slowly for people with PD (2% per year; 95% CI: 0%–4%) compared to people without PD (5% per year; 95% CI: 3%–6%). **Conclusions:** Whilst mortality in PD is only slightly increased overall, it gradually increases with advancing disease. There has been a decline in mortality in PD over time, but this decrease was less pronounced than that in the general population. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson Movement Disorder Society.

Key Words: Parkinson's disease; mortality; trends; disease progression; sociodemographic factors; primary care

Despite ongoing progress in the treatment of Parkinson's disease (PD), mortality is increased compared to the general population.[1-3] However, previous population-based studies often used prevalent cohorts with varying disease duration rather than using more informative incident cohorts followed up from diagnosis, leading to possible overestimation of mortality.[4-10] Other population-based mortality studies have included patients with progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy, which have higher mortality,[11] or were recruited from a movement disorder clinic which carries the risk of raising selection bias.[12]

Age-adjusted mortality over the age of 50 years has been decreasing in the UK over the last decade,[13,14] but there are no data on whether this is also the case for patients with PD. There have been considerable changes in the availability and use of symptomatic treatments for PD, including pharmacological, surgical, and non-pharmacological treatments, but at the present time there are no disease-modifying treatments available.[15,16] Recent treatment changes are intended to

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improve the quality of life of patients, but it is unclear whether they have also affected life expectancy. We therefore examined whether mortality of people with PD over the time period 2006–2016 has changed in a similar pattern compared to that of the general population. Estimation of survival and mortality rates are possible through analysis of data in large primary care databases that contain information on diagnoses and death, such as The Health Improvement Network (THIN). The aim of this study was to estimate trends in mortality for people with PD in the UK in comparison with people without PD in this database, and to explore associations of mortality with disease duration and sociodemographic factors.

Methods

Information from general practices in the UK contributing data to THIN during the time period January 2006–December 2016 were examined in this cohort study. We used data from practices that met the quality assurance criteria for acceptable levels of data recording[17] and acceptable standards of mortality reporting.[18] Acceptable Mortality Reporting (AMR) date is a measure of the quality of death recording in THIN. This is the year from which an individual general practice is considered to have mortality records which are proportional to that from the Office for National Statistics (ONS).[18,19] Acceptable Computer Usage (ACU) date is a quality filter to determine when a general practice was using electronic recording fully; only practices which met these quality standards were included in this study.

Data Source

The Health Improvement Network (THIN) is one of the largest longitudinal, primary care databases in the UK containing electronic medical records of more than 12 million patients (https://www.iqvia.com) and covering around 6% of the UK population.[20] It is a rich source of continuous primary care data on patients' consultations and prescribing in the UK. Information for the database is generated by collecting anonymized patient data from more than 700 participating general practices. These are generally representative of UK general practices with regard to age, gender, geographical location, and practice size.[21] Medical diagnoses and patient symptoms are recorded by general practitioners (GPs) using Read codes, a hierarchical coding system used for recording patients' clinical summary. For each individual registered with a general practice, information on age, gender, symptoms, medical diagnosis, prescriptions, and referrals to secondary care are recorded. Linked data on local area deprivation in Townsend quintiles (measure of social deprivation with Townsend quintiles from 1 [most affluent] to 5 [most deprived]) is also available, linked via the postal (zip) code to UK 2011 Census data. This is generated from a combination of measures which take into account an individual's occupation, car possession, overcrowded housing, and unemployment.[22] In addition, information on blood pressure, smoking status, height, weight, and laboratory test results are all recorded in THIN. Information on death is also available in THIN. All data are de-identified, processed, and validated by CSD Medical Research UK (https://www.iqvia.com).

Study Design

The study population included adults who were 50 + years of age and had been actively registered with a general practice for at least 6 months during the time period 1 January 2006 to 31 December 2016 (n = 3,195,391). The earliest date of PD diagnosis Read code recording or antiparkinsonian drug code recording was taken as the index date. Participants entered the cohort if they met the inclusion criteria or on the randomly matched date (index date) for individuals in the comparator group (*Non-PD Cohort*) and were followed up until they died (n = 11,198), de-registered with the GP practice (n = 14,722), or the GP practice stopped contributing data to THIN (n = 37,464), whichever was earliest. In 2003, the National Health Service South-East Multicentre Research Ethics Committee gave approval for the use of the THIN database. This study was approved by IQVIA Medical Research Scientific Review Committee in June 2019 (SRC Reference No. 19THIN034).

Inclusion and Exclusion Criteria

We excluded all people with a history of PD (prior to study entry) and those with restless leg syndrome without PD (n = 31) who were treated with dopamine agonists. In addition, individuals with diagnosis in the first 6 months after registration with a practice were excluded (n = 3756) because they could represent a recording of medical information which may be retrospective rather than a true new recording of PD.[23] For the analysis on time trends and disease duration, we started the study period 1 year from the index date only for those entering before and during 2007 to avoid follow-up time being too short for deaths to occur (Fig. S1).

The "*PD Cohort*" consisted of all adults aged 50 + years with first ever diagnosis Read code for PD and at least two prescriptions of any of five major classes of antiparkinsonian medications (levodopa-containing medications, dopamine receptor agonists, amantadine, monoamine oxidase B inhibitors [rasagiline and selegiline], and catechol-O-methyltransferase inhibitors [entacapone and tolcapone] during the time period January 2006–December 2016. This case definition has

been shown to have a validity of 90% in the General Practice Research Database (GPRD),[24] in which there is an overlap with THIN in about 60% of patients.[25] This same case definition has been used in a previous study.[26] Read code lists to identify electronic recording of PD diagnosis and drug code lists to identify the five major classes of antiparkinsonian medications were created using published guidelines.[27]

The *"General Population (Non-PD Cohort)"* comprised a frequency-matched random sample of up to six people with no record of PD. The non-PD cohort was frequency-matched within each practice on age, gender, and calendar year using a randomly assigned index date.

Outcome

The main outcome was all-cause mortality. We identified individuals who died during the follow-up through their death records in THIN.

Statistical Analysis

For descriptive purposes, we categorized mortality by calendar year, social deprivation, and 10-year age-bands: 50–59, 60–69, 70–79, 80–89, and 90+ years.

A multivariable Poisson model was used to estimate the adjusted mortality rates. Age was used as the time-scale and data on age and calendar year were split by 1-year intervals. We estimated unadjusted and mutually adjusted mortality rates and rate ratios for age, gender, calendar year, time since diagnosis or index date, smoking status, and social deprivation by PD status. We tested for multiplicative interactions between PD status and each of these variables. In order to calculate the mortality rate ratios and the marginal effects (adjusted mortality rates) adjusted for age group and other covariates, we used multivariable Poisson regression analyses. Whilst rate ratios have a baseline comparator, marginal effect on the other hand is a measurement of how much the mortality rate is predicted to vary per unit change in an exposure variable. Marginal effects for fixed values of calendar year were estimated while holding all other parameters at their observed values in the model and applying the delta method for estimation of the standard errors. We explored nonlinear relationships of mortality with age and calendar year using restricted cubic spline interpolation. We compared linear models with different spline transformations (3–5 knots) and used the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) to check whether additional knots or cubic spline transformations improved the model fit while avoiding unneeded complexity. The *P* values for categorical variables and multiplicative interaction terms were estimated by using Wald tests. We included general practice identifiers and calculated robust standard errors in order to account for the effects of clustering of observations within GP practices. Negative binomial models were run, and the outputs were compared. This allowed us to investigate overdispersion in the analyses.

All statistical analyses were conducted using Stata version 16MP (Stata Corporation, College Station, TX).

Results

Demographic Features

Within our study period of 1 January 2006 and 31 December 2016, 704 general practices met the criteria for acceptable mortality and data recording. We identified a total of 10,104 people with a diagnosis of PD (PD-cohort) with active enrolment in a general practice between the beginning 2006 and the end of 2016. There were more males in our PD cohort (60.7%). PD patients were matched with for age, gender, calendar year, and GP practice with 55,664 people without PD (non-PD cohort). The PD cohort had a lower percentage of people in the most deprived quintile (8.9% vs. 10.0%) and a lower percentage of people smoking (6.8% vs. 13.1%). In the PD cohort there were 2031 deaths while the non-PD cohort had 9167 deaths ($P < 0.001$; Table 1).

Mortality Rates

The overall unadjusted mortality rate in people with PD (PD-cohort) was 56.06 per 1000 person-years (95% CI: 53.68–58.56) and that in the non-PD cohort was 50.07 per 1000 person years (95% CI: 49.05–51.10). After adjustment for age, gender, calendar year, social deprivation, and smoking, overall mortality rate was elevated in the PD-cohort compared to the non-PD cohort (mortality rate ratio 1.14, 95% CI: 1.09–1.20) (Table 2).

Trends in Mortality Rates Over Time

The BIC favored a linear function for age whereas AIC favored a three-knot spline transformation and we have therefore reported both (Fig. 1). There was an interaction between PD status and calendar year (*P* value for interaction in spline transformed model = 0.0005). Adjusted mortality rates in the PD group declined over time by around 2% per year or 1.2 per 1000 person-years. However, adjusted mortality rates in the non-PD group decreased more dramatically at 5% per year or 2.4 per 1000 person-years over the time period observed. Further adjustment for smoking status and social deprivation had no meaningful impact on the estimates.

There were also strong interactions between PD status and time since diagnosis/index date (*P* value for

TABLE 1 *Baseline characteristics for Parkinson's disease (PD) and non-PD cohort*

Variable	PD cohort (n = 10,104)	Non-PD cohort (n = 55,664)	*P value
Died, n	2031	9167	<0.001
Gender, n (%)			
Men	6135 (60.72)	33,778 (60.68)	0.945
Women	3969 (39.28)	21,886 (39.32)	
Age group (y), n (%)			
50–59	790 (7.82)	4403 (7.91)	0.705
60–69	2328 (23.04)	12,961 (23.29)	
70–79	4187 (41.46)	23,172 (41.63)	
80–89	2554 (25.28)	13,941 (25.05)	
>90	245 (2.40)	1187 (2.31)	
Townsend score			
1 (least deprived)	2811 (27.82)	13,746 (24.69)	<0.001
2	2320 (22.96)	12,399 (22.27)	
3	1901 (18.81)	10,815 (19.43)	
4	1441 (14.26)	8728 (15.68)	
5 (most deprived)	895 (8.86)	5565 (10.00)	
Missing data	736 (7.28)	4411 (7.92)	
Smoking status			
Non-smoker	5500 (54.43)	24,501 (44.02)	<0.001
Ex-smoker	3126 (30.94)	18,624 (33.46)	
Current smoker	690 (6.83)	7280 (13.08)	
Missing data	788 (7.80)	5259 (9.45)	

Abbreviations: PD, Parkinson's disease; y, years.
*Chi-squared test.

TABLE 2 *Overall mortality rates and ratios in the Parkinson's disease (PD) and non-PD groups*

Parameter	General population (non-PD cohort) (n = 55,664)	PD cohort (n = 10,104)	*P* value
Deaths, n	9167	2031	<0.001
PY per 1000 (95% CI)	183.09	36.23	
Rate per 1000 PY (95% CI)	50.07 (49.05 to 51.10)	56.06 (53.68 to 58.56)	
Unadjusted mortality rate ratio	1 (Reference)	1.12 (1.07 to 1.17)	<0.001
Age, gender, calendar year, social deprivation, smoking adjusted mortality rate ratio (95% CI)	1 (Reference)	1.14 (1.09 to 1.20)	<0.001

Abbreviations: PD, Parkinson's disease; PY, person-years; CI, confidence interval.

interaction <0.0001). Adjusted mortality rates per 1000 person-years were lower in people with PD than the general population in the year following diagnosis (Fig. 2), but gradually increased with each year from 43 (95% CI: 38–48) in the first year to 75 (95% CI: 64–85) at 5 years after diagnosis (Fig. 2 and Table S2). Conversely, adjusted mortality rates were decreasing in the non-PD cohort during their follow-up from index date, resulting in a gradually increasing mortality rate ratio with increasing years after diagnosis ($P < 0.001$;

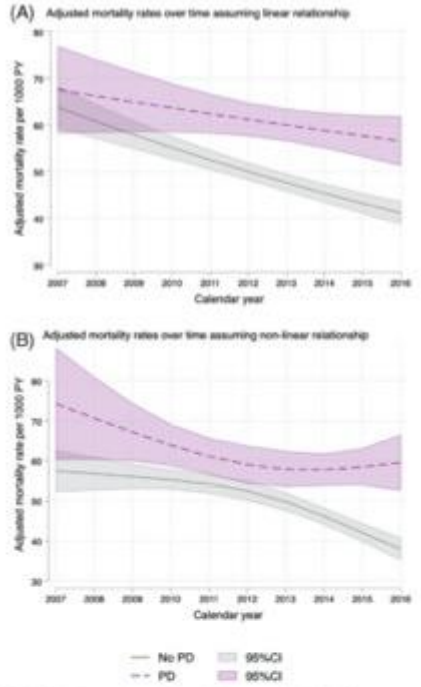

FIG. 1. Mortality over time: (**A**) on the linear scale adjusted for age, gender, social deprivation, and smoking; (**B**) on the nonlinear scale adjusted for age, gender, social deprivation, and smoking. PY, person-years; PD, Parkinson's disease; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

Fig. 2 and Table S2). We further examined time trends separately by year since diagnosis/index date up to 4 years since diagnosis/index date. There was no strong evidence of nonlinearity for calendar year within years since diagnosis/index date, and due to low number of events we only explored up to year 4. In the first year, overall mortality rates were lower in people with PD and declined at a similar rate to those without PD. However, we found that a differential decline in mortality rates was seen in the more recent years of data collection for PD patients more than 2 years into their diagnosis (Fig. S2).

In order to account for immortal time bias, we conducted a sensitivity analysis where start of follow-up was moved to the latest date of PD diagnosis using Read code recording or antiparkinsonian drug code.[28,29] This showed no meaningful change in the results (Fig. S3).

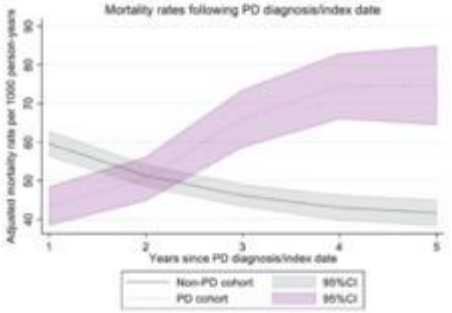

FIG. 2. Mortality rates following Parkinson's disease diagnosis/index date adjusted for age, gender, calendar year, social deprivation, and smoking. PD, Parkinson's disease; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

Other Factors Associated with Increased Mortality Rates

Adjusted mortality rates increased with age at a broadly similar rate for people with and without PD (Table 3 and Fig. S4) (P value for interaction spline transformed model = 0.89). Men in both groups had similarly higher adjusted mortality rates compared to women (P value for interaction = 0.45) (Table 3). Adjusted mortality rates increased similarly with social deprivation in both groups and smoking status was also associated with increased mortality in both groups. There was some evidence that the differences in mortality rates for people with and without PD were more pronounced in the least deprived areas and in non/former smokers; however, the differences were small (Table 3).

In order to examine whether the validated but stringent PD inclusion criteria introduced selection bias and limited the generalizability of the findings, we also examined the differences in demographic characteristics when loosening the inclusion criteria from PD code plus two prescriptions to PD code plus one prescription and PD diagnosis code only. The sociodemographic characteristics were broadly similar across included/excluded groups although the more stringent criteria seemed to include more younger people and men (Table S3).

Discussion

In this large, population-based study of more than 10,000 patients with PD and more than 50,000 in the control group without PD, the mortality rate ratio in the PD cohort was 1.14 times that of the general population indicating a modest overall increase in mortality associated with the condition. The mortality rate ratio

TABLE 3 *Adjusted mortality rates by age group, gender calendar year, social deprivation, and smoking*

	PD cohort				Non-PD cohort						
Variable	Events	Person-years (1000)	[a]Adjusted mortality rate (95% CI)	*P* value	Events	Person-years (1000)	[a]Adjusted mortality rate (95% CI)	*P* value	Mortality rate ratio	[b]*P* value	[c]*P* value
Age group, y											
50–59	14	2.09	6.98 (3.0 to 10.97)	<0.001	51	10.63	4.46 (3.30 to 5.62)	<0.001	1.48 (0.80 to 2.76)	0.212	0.474
60–69	107	7.74	14.20 (11.30 to 17.09)		521	38.41	13.04 (11.81 to 14.27)		1.08 (0.87 to 1.33)	0.497	
70–79	571	14.95	39.57 (35.98 to 43.16)		2537	74.70	33.53 (31.90 to 35.16)		1.17 (1.07 to 1.28)	0.001	
80–89	1052	10.34	105.75 (98.78 to 112.71)		4813	53.35	92.91 (89.23 to 96.59)		1.14 (1.07 to 1.22)	<0.001	
>90	287	1.09	283.69 (250.05 to 321.32)		1245	5.97	223.98 (209.40 to 238.55)		1.28 (1.12 to 1.45)	<0.001	
Gender											
Male	1288	21.65	65.99 (61.77 to 70.20)	<0.001	5792	109.53	54.76 (52.41 to 57.12)	<0.001	1.18 (1.11 to 1.25)	<0.001	0.452
Female	743	14.58	51.82 (47.48 to 56.17)		3375	73.39	44.71 (42.67 to 46.74)		1.14 (1.06 to 1.23)	0.001	
Townsend quintile											
1 (least deprived)	510	10.37	55.65 (50.21 to 61.09)	0.0197	1939	47.19	44.25 (41.53 to 46.98)	<0.001	1.24 (1.13 to 1.37)	<0.001	0.323
2	482	8.54	58.85 (53.02 to 64.68)		2023	41.57	48.77 (45.90 to 51.64)		1.19 (1.08 to 1.32)	0.001	
3	404	6.69	66.03 (59.30 to 72.75)		1919	35.70	53.56 (50.29 to 56.83)		1.19 (1.08 to 1.32)	0.001	
4	291	5.05	61.08 (53.75 to 68.40)		1636	27.52	56.51 (52.48 to 60.54)		1.04 (0.92 to 1.18)	0.497	
5 (most deprived)	210	3.0	67.88 (57.89 to 77.87)		1049	17.67	59.36 (54.55 to 64.17)		1.09 (0.94 to 1.26)	0.246	
Missing data	134				607						
Smoking status											
Non-smoker	1035	20.40	53.87 (50.24 to 57.50)	<0.001	3649	82.57	44.21 (42.10 to 46.32)	<0.001	1.18 (1.11 to 1.26)	<0.001	0.086
Ex-smoker	716	10.76	65.14 (59.85 to 70.43)		3450	60.03	54.02 (51.62 to 56.43)		1.19 (1.10 to 1.28)	<0.001	
Current smoker	149	2.50	74.24 (61.70 to 86.78)		1378	23.88	74.74 (69.82 to 79.66)		0.96 (0.80 to 1.13)	0.604	
Missing data	131				690						

Abbreviations: PD, Parkinson's disease; CI, confidence interval; y, years.
[a]Adjusted for age, gender calendar year, social deprivation, and smoking.
[b]Wald test for categorical variable.
[c]Wald test for multiplicative interaction.

in this study is within the range reported in the literature, but at the lower end of the previous published mortality results. In previous studies mortality ratios in people with PD have been reported to range from 0.9 to 3.8.[1] Whilst in the lower range it is comparable to recent incident clinical and community-based cohort studies which have also reported similar mortality ratios.[1,30,31] Previous register-based or population-based studies[4,7,8,10,32-35] with higher rate ratios have included both incident and prevalent cases,[7] while others included prevalent PD cases which are likely to have higher mortality than newly diagnosed PD cases. These cases are likely to have longer disease duration and severe disease resulting in higher mortality.[4,8,10,32,33,35,36] Other population-based studies[31,37-39] on survival of incident patients with PD are limited by small number of cases[31,36,39] and often also included people with other causes of parkinsonism such as multiple system atrophy, corticobasal degeneration, or progressive supranuclear palsy which have been reported to have higher mortality.[11]

Our findings suggested that men with PD had a slightly higher mortality over women with PD, but the difference was small and not different to the control group without PD. Previously, a Sydney multicentre study showed no differences in the sexes[40] but other studies have reported increased mortality in men with PD compared to women with PD[4,41] There are speculations that female sex hormones (estrogens) have some neuroprotective effect on neuronal cell death,[42] and reports of animal studies showed that the potential beneficial effect of estrogens is probably due to their antioxidant effects.[43] Other available data are conflicting[43-46] and further large observational studies are proposed. We also found no strong differences in mortality between people with and without PD as regards influence of lower socioeconomic status and smoking in this study, both of which are associated with increased mortality.[47]

In comparison to the general population, mortality rates were lower in patients with PD than the general population in the year following diagnosis, but gradually increased in patients with PD with longer disease duration, with the excess mortality of people with PD continuing to increase with each year after the diagnosis of PD. It is possible that patients who present with symptoms leading to diagnosis of PD receive greater medical attention and more investigations at the time of diagnosis, although referral bias due to patients with short life expectancy not being referred cannot be excluded. However, increasing disease progression with advancing disease was associated with higher mortality. This has been reported in a recent systematic review on mortality in PD in which rate ratios are reported to increase with disease duration.[1] In the Rotterdam study, mortality was reported to increase with disease duration with ratios increasing by 1.03 (95% CI: 0.99–1.07) per year.[7] Another study from the USA, however, reported increased mortality risk across all categories of disease duration including disease duration below 2 years (rate ratio 2.0, 95% CI: 1.03–3.88).[48] The reason for this increasing mortality rate in PD with longer disease duration may be comorbidities, increasing disease severity, or complications of PD. These will need to be identified and addressed in order to develop interventions to reduce mortality in PD.[41]

During our follow-up period, adjusted mortality rates per 1000 person-years in people with PD declined slightly from 69 (95% CI: 60–79) in 2007 to 59 (95% CI: 53–64) in 2016. This is in keeping with previous studies in the UK, which showed a steady slight decline in mortality in PD between 1993 and 2006[49] as well as earlier periods.[50,51] Conversely, recent research from Northern Italy[52] showed an increasing trend in mortality of people with PD from 1.9% in 2008 to 2.4% in 2015. This study was based on a shorter interval and was limited by mortality records as the authors included other types of parkinsonism (with higher mortality) in their analysis and reported that they could not ascertain the specificity of PD in death certificates leading to possible overestimation of PD mortality. Differences in healthcare systems in different countries could also have contributed to differences in PD mortality.

However, in our study mortality rates per 1000 person-years at risk in the general population fell from 63 (95% CI: 58–67) in 2007 to 41 (95% CI: 39–44) in 2016 over time in keeping with the previously reported declining mortality rates during that decade. Reports from ONS[13] and Public Health England[14] showed a significant decline in age-specific mortality rates in both men and women aged 50+ years in the UK population between 2006 and 2016. The explanation for this reduction in mortality was attributed to falling rates from cardiovascular diseases. As there was a slower decline in mortality rate in the PD group, this resulted in an increasing mortality interval between patients with PD and the control population over that time period. These data suggest that improvement in mortality in the age group 50+ years in the general population is not seen in the same way in people with PD. It is possible that interventions leading to lower cardiovascular death rates are either not implemented or as effective to the same degree in patients with PD. Alternatively, the process of PD itself is the primary determinant of mortality, particularly in advancing disease, and therefore overshadows improvements in cardiovascular or other health. This interpretation is supported by our subanalysis of mortality within fixed time periods, which suggested that the increase in the mortality gap is particularly seen with longer disease duration. There are very few comparable studies. In a previous study in Ontario, Canada from 1996 to 2013

the mortality in people with PD declined by 5.5% over 18 years.[53] Whilst this study did not include a control group, precluding a direct comparison with mortality in the general population, the authors reported that mortality in the general population had previously been found to have decreased by 19% during a similar time period.[53]

Strength and Limitations

The main strength of this study is the prospective design with a follow-up of 10 years using data from a large primary care database (THIN) which is generalizable to people with PD living in the UK. This database has provided information on mortality of the PD cohort and the comparator non-PD cohort which were derived from the UK general population. Another strength of our study is that we evaluated mortality in newly diagnosed cases (incident cohort) of PD rather than prevalent cases which may lead to overestimation of rate ratios. It is reported that use of prevalent cases may cause higher estimates of rate ratios.[36] This suggests that our relatively low mortality rates represent a better estimate for the overall population of patients with PD. In addition, a range of possible demographic and health confounders that could distort the results were taken into consideration while developing our robust statistical approach for analyzing mortality data in this cohort study.

There are, however, limitations with respect to analysis of routine healthcare data. We cannot rule out underdiagnosis of PD as registration in the database requires health-seeking behavior as well as diagnosis and those who do not attend a GP practice may be missed. Another limitation of this study is that we did not examine these patients but relied on GP codes for PD for clinical diagnoses which may result in misclassification of PD cases. However, the validity of significant diagnoses in primary care databases is high,[54,55] including for PD,[24] and in most instances this will be recorded following a diagnosis made in secondary care. In any observational study using routine data the potential for residual confounding cannot be ruled out. In particular we were unable to include factors such as ethnicity or some social factors (eg, having a carer, marital status) due to the high number of missing data. Nevertheless, adjustment for smoking and socioeconomic status as confounders in addition to age- and gender-standardized mortality rate ratios increased the applicability of the results from this study.

Conclusions

Our large population-based cohort study found that mortality rates in PD in the UK between 2006 and 2016 were slightly increased compared to the general population but mortality trends across gender, age, smoking status, and social deprivation were broadly similar to people without PD. Mortality was lower than in the general population in the year of diagnosis but increased year on year with longer disease in people with PD. Whilst overall mortality rates slightly declined in the PD group over the 10-year time period studied, mortality rates in people without PD declined at a faster rate leading to a relatively large differential in the most recent year of data (2016). These data suggest that progression of PD is associated with increasing mortality and that a decrease in mortality will require treatments to address the underlying disease progression, complications, or associated comorbidities. ■

Acknowledgments: THIN is a registered trademark of Cegedim SA in the UK and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as part of their routine primary care.

Data Availability Statement

The authors have obtained the data for this study from IQVIA through a research license and do not own the dataset used and do not have permission to share the data. Access to THIN can be obtained through IQVIA by applying for a research license. More information on the availability of THIN data is available in the following URL https://www.iqvia.com/locations/uk-and-ireland/thin and permissions for data access can be obtained through https://www.iqvia.com/contact/general. The authors accessed the data in the same manner and had no special privileges to the data.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Appendices 5-2 to 5-14: Supplementary tables and figures from PD mortality study.

Appendix 5-2: Table 5-1 Demographic characteristics of people with PD using different diagnostic definitions.

Variables	PD diagnosis Read code	PD diagnosis Read code plus 1 drug prescription	PD diagnosis Read code plus 2 drug prescriptions (prior to study follow-up)	PD diagnosis Read code plus 2 drug prescriptions
Gender *n (%)*				
Men (%)	173(56.9)	792(59.7)	2,054(54.7)	6,135(60.7)
Women (%)	117(43.1)	600(40.3)	1,702(45.3)	3,969(39.3)
Age group *n (%)*				
50 to 59	78(5.7)	18(6.21)	327(8.9)	790(7.82)
60 to 69	282(20.5)	46(15.9)	856(23.3)	2,328(23.0)
70 to 79	507(36.8)	104(35.9)	1,387(37.7)	4,187(41.5)
80 to 89	442(32.2)	106(36.6)	999(27.1)	2,554(25.3)
90 and over	66(4.80)	16(5.5)	113(3.1)	242(2.4)
Townsend quintile				
1(least deprived)	331(23.8)	87(30.0)	838(22.3)	2,811(27.8)
2	325(23.4)	69(23.8)	895(23.8)	2.320(23.0)
3	257(18.5)	41(14.1)	673(17.9)	1,901(18.8)
4	225(16.2)	41(14.1)	583(15.5)	1,441(14.3)
5(most deprived)	136(9.77)	36(12.4)	355(9.5)	895(8.7)
Not recorded	118(8.5)	16(5.5)	412(10.9)	736(7.3)

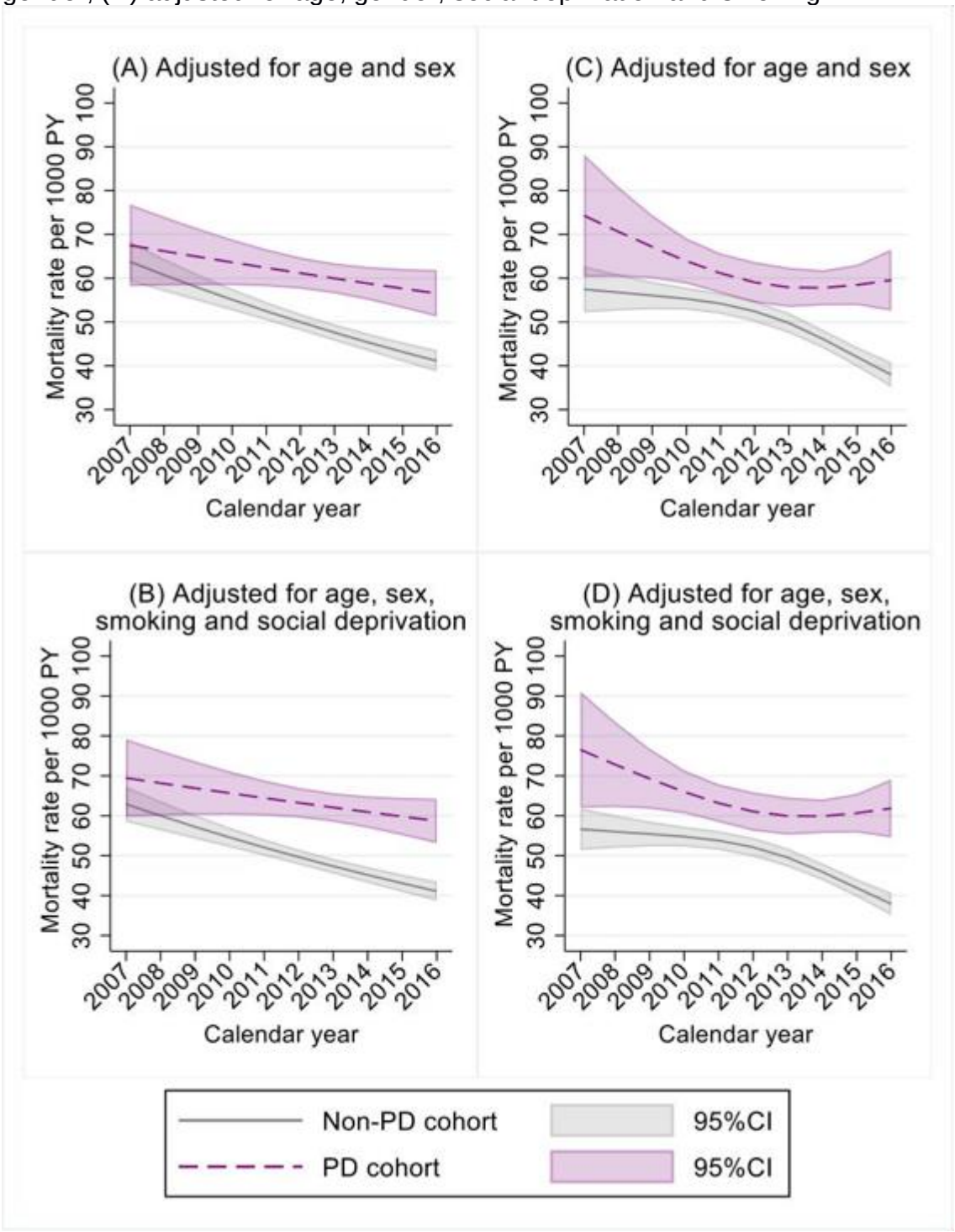
Appendix 5-3: Table 5-2: Unadjusted mortality rates in the PD and non-PD groups

	PD-cohort			Non-PD cohort		
	Events	Person-Years (1000)	Mortality rate (95% CI)	Events	Person-Years	Mortality rate (95% CI)
Overall	2,031	36.23	56.06 (53.68 to 58.56)	9,167	183.09	50.07 (49.05 to 51.10)
Age group						
50 to 59	14	2.09	6.70 (3.97 to 11.31)	51	10.63	4.80 (3.65 to 6.32)
60 to 69	107	7.74	13.82 (11.43 to 16 70)	521	38.41	13.56 (12.45 to 14.78)
70 to 79	571	14.95	38.19 (35.18 to 41.45)	2,537	74.70	33.96 (32.67 to 35.31)
80 t0 89	1,052	10.34	101.67 (95.71 to 108.0)	4,813	53.35	90.21 (87.70 to 92.80)
>90	287	1.09	263.42 (234.59 to 295.79)	1,245	5.97	206.77 (195.55 to 218.63)
Gender						
Male	1,288	21.65	59.50 (56.34 to 62.84)	5,792	109.53	52.80 (51.46 to 54.18)
Female	743	14.58	50.96 (47.43 to 54.76)	3,375	73.39	46.0 (44.46 to 47.56)
Year						
2007	22	0.43	51.47 (33.89 to 78.16)	112	1.96	57.28 (47.60 to 68.93)
2008	92	1.76	52.27 (42.62 to 64.14)	512	7.84	62.28 (59.86 to 71.18)
2009	135	3.01	44.86 (37.90 to 53.11)	775	13.14	58.96 (54.94 to 63.26)
2010	208	3.59	57.87 (50.52 to 66.30)	906	15.96	56.77 (53.19 to 60.58)
2011	209	4.09	51.08 (44.61 to 58.50)	951	19.13	49.71 (46.65 to 52.97)
2012	267	4.49	59.44 (52.72 to 67.02)	1167	22.21	52.53 (49.60 to 55.63)
2013	275	4.66	59.00 (52.43 to 66.41)	1171	24.27	48.26 (45.57 to 51.10)
2014	286	4.65	61.45 (54.72 to 69.00)	1133	25.61	44.24 (41.74 to 46.89)
2015	273	4.14	65.87 (58.50 to 74.17)	1007	23.49	42.88 (40.31 to 45.61)
2016	210	3.49	60.10 (52.50 to 68.81)	703	20.58	34.16 (31.72 to 36.78)
Townsend quintile						
1	510	10.37	49.18 (45.10 to 53.64)	1,939	47.19	41.09 (39.30 to 42.96)
2	482	8.54	56.44 (51.62 to 61.71)	2,023	41.57	48.67 (46.59 to 50.83)
3	404	6.69	60.43 (54.81 to 66.62)	1,919	35.70	53.76 (51.40 to 56.21)
4	291	5.05	57.68 (51.42 to 64.70)	1,630	27.52	59.23 (56.42 to 62.18)
5	210	3.0	70.28 (61.39 to 80.46)	1,049	17.67	59.38 (55.89 to 63.08)
No records	134			607		
Smoking status						
Non-smoker	1035	20.40	50.74 (47.74 to 53.92)	3649	82.57	44.19 (42.78 to 45.65)
Ex-smoker	716	10.76	66.52 (61.83 to 71.58)	3450	60.03	60.03 (55.58 to 59.42)
Current smoker	149	2.50	59.55 (50.72 to 69.92)	1378	23.88	23.88 (54.74 to 60.84)
No records	131			690		
Year(s) after PD diagnosis						
First year	329	9.44	34.84 (31.27 to 38.81)	2959	48.83	60.60 (58.45 to 62.82)
Second year	362	7.64	47.40 (42.76 to 52.54)	1,926	37.73	51.05 (48.82 to 53.38)
Third year	354	5.95	59.49 (53.61 to 66.03)	1,343	29.10	46.16 (43.75 to 48.69)
Fourth year	298	4.48	66.54 (59.39 to 74.54)	943	21.9	43.06 (40.40 to 45.90)

Fifth year	238	3.25	73.16 (64.43 to 83.07)	741	16.23	45.66 (42.49 to 49.07)
Sixth year	180	2.29	78.74 (68.04 to 91.13)	519	11.56	44.90 (41.20 to 48.93)
Seventh year	134	1.49	89.84 (75.85 to 106.41)	314	7.83	40.11 (35.91 to 44.80)
Eight year	73	0.91	80.54 (64.03 to 101.31)	199	5.06	39.35 (34.25 to 45.22)
Ninth year	38	0.49	76.91 (55.96 to 105.70)	147	3.01	48.87 (41.57 to 57.44)
Tenth year	20	0.22	89.05 (57.45 to 138.02)	54	1.44	37.51 (28.73 to 48.97)

PD-Parkinson’s disease

Appendix 5-4: Figure 5-1: Mortality over time: on the linear scale: (A) adjusted for age and gender, (B) adjusted for age, gender, social deprivation and smoking; Mortality over time on the non-linear scale: (C) adjusted for age and gender, (D) adjusted for age, gender, social deprivation and smoking.



Appendix 5-5: Table 5-3: Adjusted mortality rates (adjusted for age, gender, calendar year and social deprivation) following PD diagnosis/index date for non-PD group.

Variables	PD cohort		Non-PD cohort				
	*Adjusted Mortality rate (95% CI)	**p-value	*Adjusted Mortality rate (95% CI)	**p-value	Mortality rate ratio	**p-value	***p-value
Years following diagnosis/ index date							
First year	35.34 (31.20 to 39.49)	<0.001	63.39 (60.02 to 66.77)	<0.001	0.56 (0.50 to 0.63)	<0.001	<0.001
Second year	50.20 (44.66 to 55.74)		52.81 (49.84 to 55.78)		0.90 (0.80 to 1.01)	0.065	
Third year	61.38 (54.37 to 68.40)		47.38 (44.36 to 50.40)		1.28 (1.14 to 1.44)	<0.001	
Fourth year	67.57 (59.31 to 75.82)		43.55 (40.33 to 46.77)		1.58 (1.38 to 1.81)	<0.001	
Fifth year	72.87 (63.04 to 82.70)		45.29 (41.49 to 49.10)		1.70 (1.47 to 1.96)	<0.001	
Sixth year	77.61 (65.15 to 90.07)		43.62 (39.91 to 47.33)		1.92 (1.62 to 2.28)	<0.001	
Seventh year	84.40 (69.41 to 99.39)		38.63 (34.02 to 43.23)		2.44 (2.00 to 2.97)	<0.001	
Eight year	76.27 (58.81 to 93.72)		37.89 (32.26 to 43.52)		2.35 (1.79 to 3.08)	<0.001	
Ninth year	74.76 (51.25 to 98.26)		46.54 (38.51 to 54.58)		1.96 (1.37 to 2.81)	<0.001	
Tenth year	87.12 (48.0 to 126.26)		36.81 (26.76 to 46.87)		3.05 (1.82 to 5.14)	<0.001	

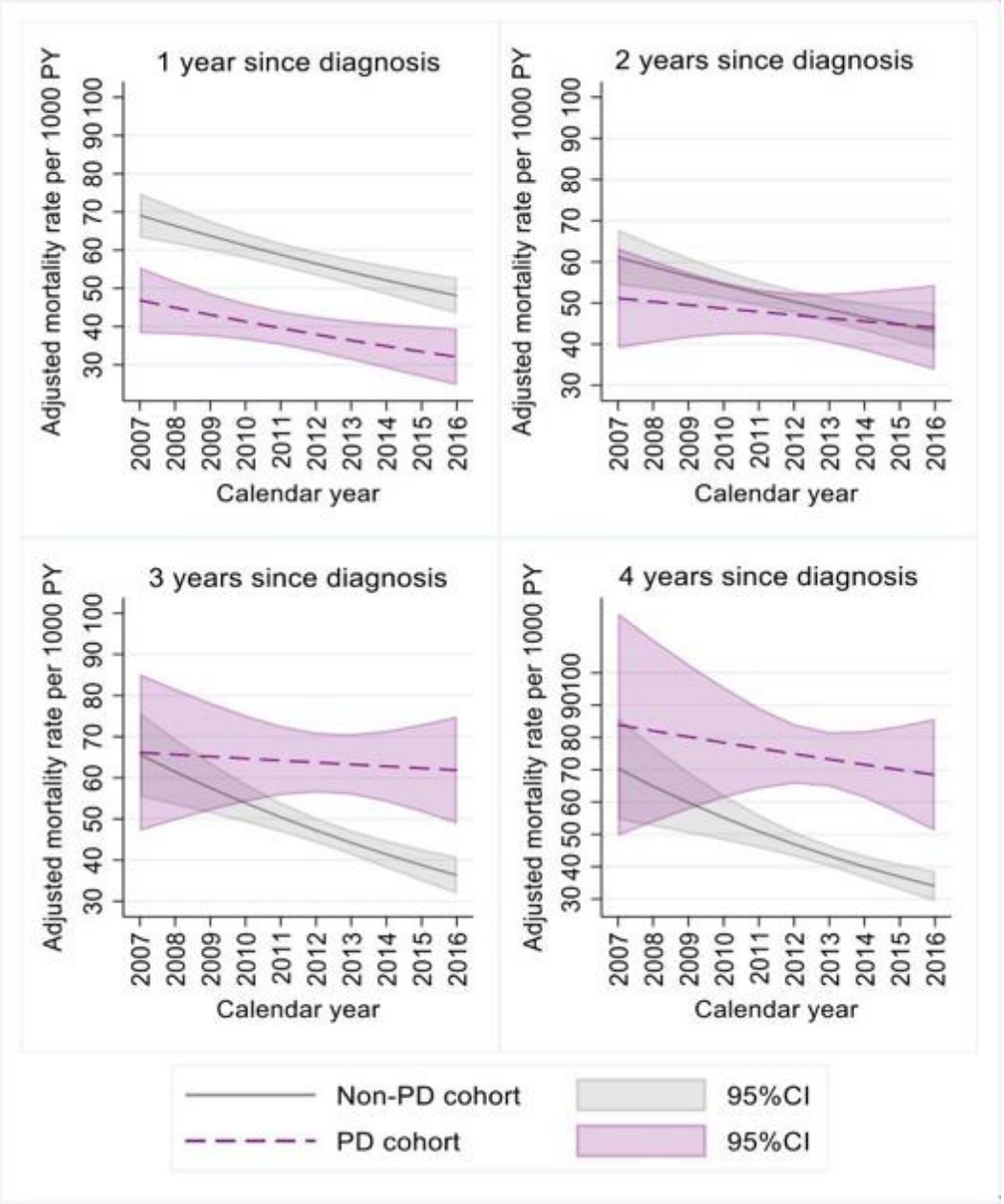
PD-Parkinson's disease. *Adjusted for age, gender, calendar year and social deprivation. **Wald test for categorical variable. ***Wald test for multiplicative interaction.

Appendix 5-6: Table 5-4: Adjusted mortality rates (adjusted for age, gender, calendar year, social deprivation and smoking) following PD diagnosis/index date for non-PD group.

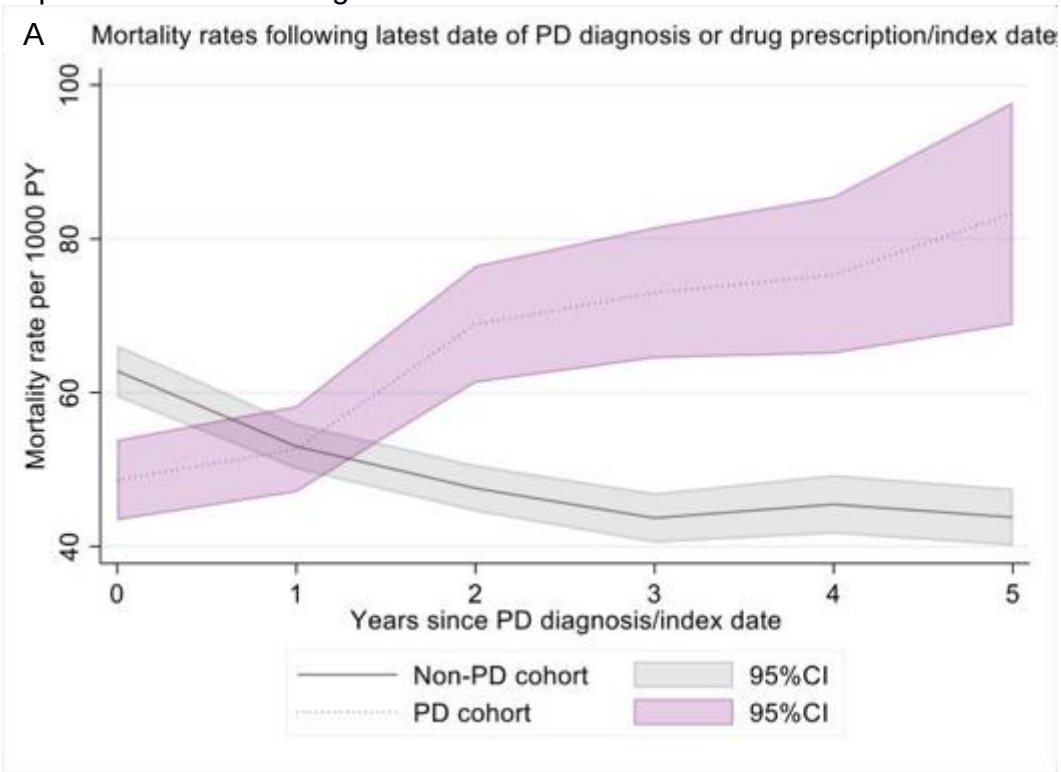
Variables	**PD cohort**		**Non-PD cohort**				
	*Adjusted Mortality rate (95% CI)	**p-value	*Adjusted Mortality rate (95% CI)	**p-value	Mortality rate ratio	**p-value	***p-value
Years following diagnosis/ index date							
First year	43.46 (38.43 to 48.48)	<0.001	59.62 (56.34 to 62.90)	<0.001	0.70 (0.63 to 0.78)	<0.001	<0.001
Second year	50.56 (44.88 to 56.24)		51.35 (48.46 to 54.23)		0.96 (0.86 to 1.07)	0.499	
Third year	66.13 (58.68 to 73.58)		46.20 (43.31 to 49.09)		1.42 (1.26 to 1.60)	<0.001	
Fourth year	74.48 (66.02 to 82.93)		43.06 (39.78 to 46.35)		1.74 (1.54 to 1.98)	<0.001	
Fifth year	74.66 (64.46 to 84.87)		41.69 (38.27 to 45.11)		1.84 (1.59 to 2.12)	<0.001	
Sixth year	88.69 (74.43 to 102.95)		40.62 (36.54 to 44.69)		2.27 (1.92 to 2.71)	<0.001	
Seventh year	87.58 (70.32 to 104.84)		37.13 (32.44 to 41.83)		2.51 (2.01 to 3.13)	<0.001	
Eighth year	73.21 (52.41 to 94.00)		42.06 (35.72 to 48.41)		1.89 (1.37 to 2.59)	<0.001	
Ninth year	94.00 (58.84 to 129.07)		32.01 (24.43 to 39.59)		3.23 (2.11 to 4.94)	<0.001	
Tenth year	94.26 (9.79 to 178.74)		46.05 (28.06 to 64.03)		2.26 (0.82 to 6.24)	0.100	

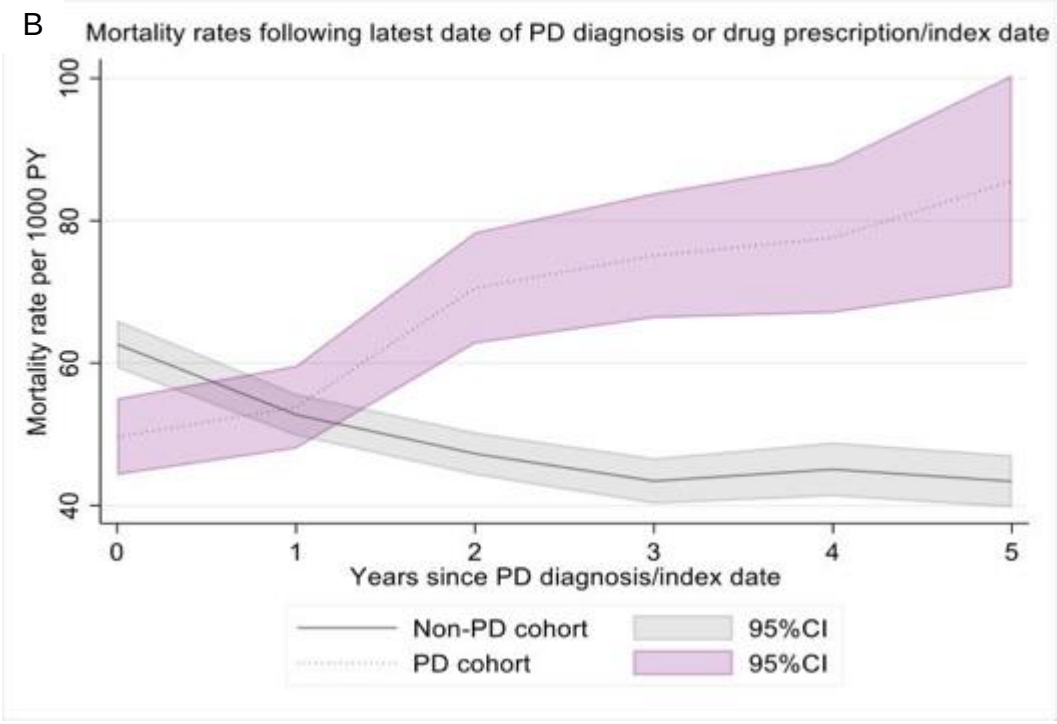
PD-Parkinson's disease. *Adjusted for age, gender, calendar year and social deprivation. **Wald test for categorical variable. ***Wald test for multiplicative interaction.

Appendix 5-7: Figure 5-2: Mortality rate over time adjusted for age, gender, time since diagnosis/index date, by follow-up year since diagnosis/entry.



Appendix 5-8: Figure 5-3: Sensitivity analysis showing (A) mortality rates following PD diagnosis/drug prescription/index date adjusted for age, gender, calendar year and social deprivation; (B) mortality rates following PD diagnosis/ drug prescription/index date adjusted for age, gender, calendar year, social deprivation and smoking.





Appendix 5-9: Table 5-5: Adjusted mortality rates by age group and gender.

Variables	PD cohort		Non-PD cohort				
	*Adjusted Mortality rate (95% CI)	**p-value	*Adjusted Mortality rate (95% CI)	**p-value	Mortality rate ratio	**p-value	***p-value
Age group							
50 to 59	6.77 (2.88 to 10.65)	<0.001	4.66 (3.44 to 5.87)	<0.001	1.37 (0.74 to 2.55)	0.321	0.3391
60 to 69	13.79 (11.01 to 16.57)		13.38 (12.11 to 14.65)		1.01 (0.81 to 1.25)	0.946	
70 to 79	38.52 (35.10 to 41.93)		33.86 (32.22 to 35.50)		1.11 (1.01 to 1.22)	0.024	
80 to 89	102.87 (96.33 to 109.42)		92.05 (88.39 to 95.71)		1.11 (1.04 to 1.18)	0.002	
>90	275.77 (241.98 to 309.56)		216.27 (202.23 to 230.30)		1.25 (1.10 to 1.41)	0.001	
Gender							
Male	65.48 (61.33 to 69.64)	<0.001	55.88 (53.50 to 58.25)	<0.001	1.14 (1.07 to 1.20)	<0.001	0.397
Female	49.58 (45.51 to 53.65)		44.16 (42.15 to 46.17)		1.09 (1.01 to 1.18)	0.023	

PD-Parkinson's disease. *Adjusted for age, gender and calendar year **Wald test for categorical variable. ***Wald test for multiplicative interaction.

Appendix 5-10: Table 5-6: Adjusted mortality rates by age group, gender and social deprivation.

Variables	PD cohort		Non-PD cohort				
	*Adjusted Mortality rate (95% CI)	**p-value	*Adjusted Mortality rate (95% CI)	**p-value	Mortality rate ratio	**p-value	***p-value
Age group							
50 to 59	6.80 (2.91 to 10.70)	<0.001	4.64 (3.43 to 5.85)	<0.001	1.39 (0.75 to 2.59)	0.297	0.357
60 to 69	13.87 (11.07 to 16.68)		13.42 (12.15 to 14.69)		1.02 (0.82 to 1.26)	0.880	
70 to 79	38.79 (35.34 to 42.24)		33.80 (32.16 to 35.44)		1.13 (1.03 to 1.23)	0.012	
80 to 89	103.11 (96.53 to 109.68)		91.64 (88.04 to 95.25)		1.11 (1.04 to 1.19)	0.001	
>90	276.84 (242.88 to 310.79)		215.31 (201.41 to 229.21)		1.25 (1.10 to 1.43)	0.001	
Gender							
Male	65.99 (61.82 to 70.17)	<0.001	56.13 (53.75 to 58.51)	<0.001	1.15 (1.08 to 1.22)	<0.001	0.407
Female	49.56 (45.50 to 53.63)		43.74 (41.75 to 45.74)		1.10 (1.02 to 1.19)	0.013	
Townsend quintile							
1(least deprived)	54.14 (48.83 to 59.45)	0.0082	43.43 (40.78 to 46.09)	<0.001	1.22 (1.11 to 1.34)	<0.001	0.252

2	57.07 (51.58 to 62.57)	48.69 (45.82 to 51.57)	1.14 (1.03 to 1.26)	0.010
3	65.04 (58.47 to 71.60)	54.06 (50.75 to 57.38)	1.16 (1.04 to 1.28)	0.006
4	60.76 (53.49 to 68.03)	57.74 (53.63 to 61.86)	1.01 (0.90 to 1.14)	0.836
5(most deprived)	68.09 (58.06 to 78.11)	62.13 (57.08 to 67.18)	1.05 (0.90 to 1.21)	0.547

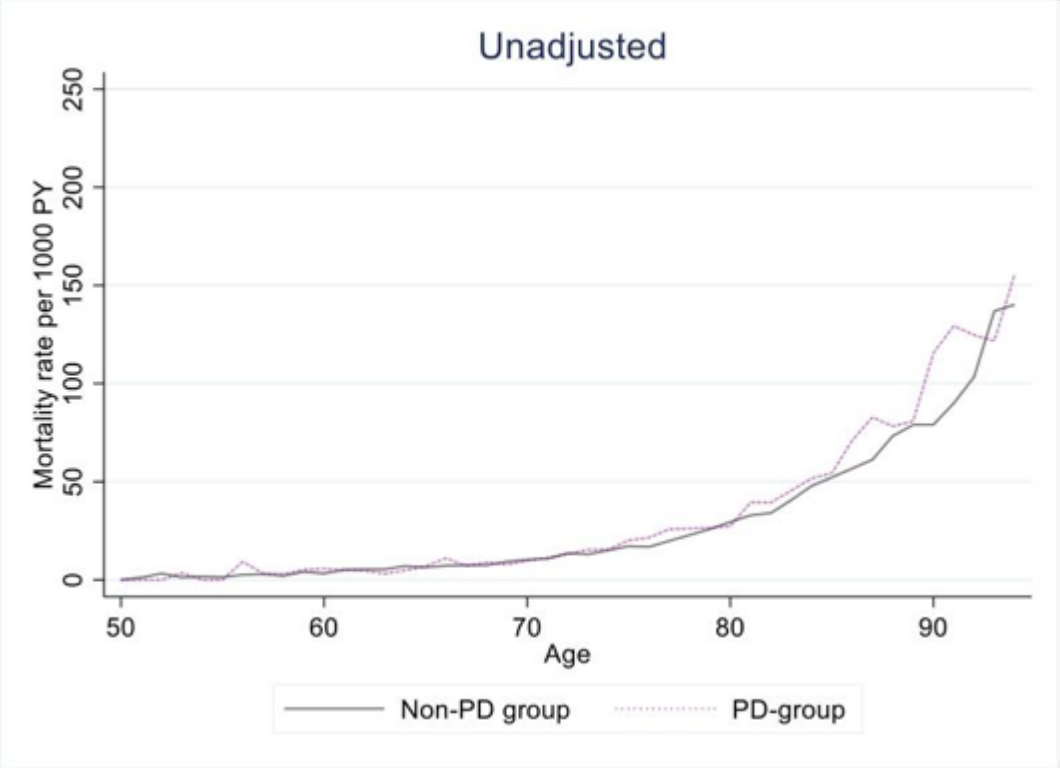
PD-Parkinson's disease. *Adjusted for age, gender and calendar year **Wald test for categorical variable. ***Wald test for multiplicative interaction.

Appendix 5-11: Table 5-7: Adjusted mortality rates by age group, gender, social deprivation and smoking.

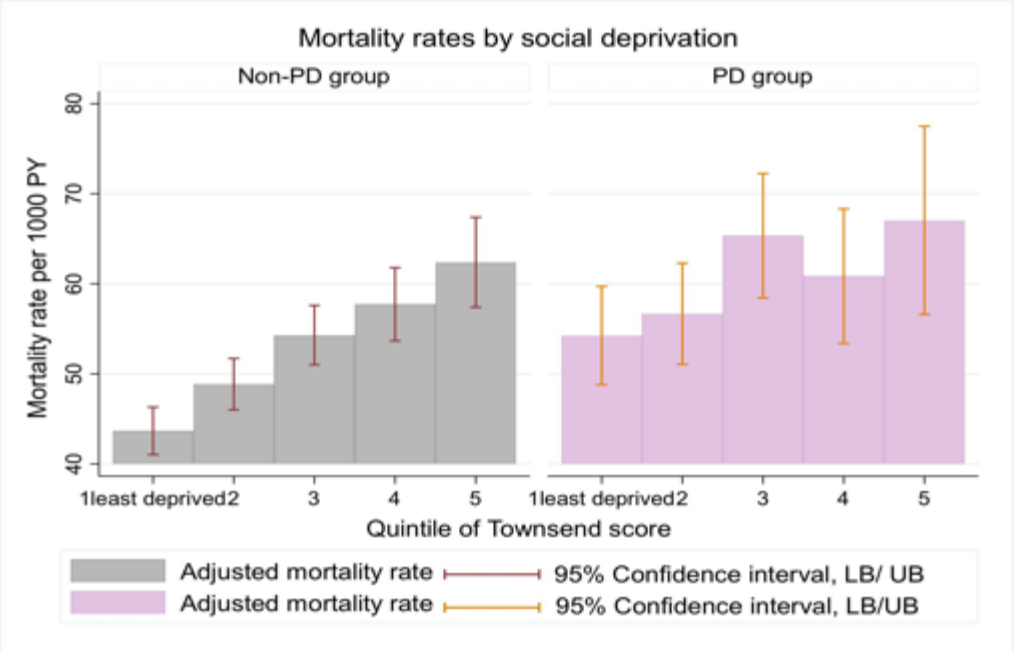
Variables	PD cohort		Non-PD cohort				
	*Adjusted Mortality rate (95% CI)	**p-value	*Adjusted Mortality rate (95% CI)	**p-value	Mortality rate ratio	**p-value	***p-value
Age group							
50 to 59	6.99 (3.0 to 10.99)	<0.001	4.47 (3.31 to 5.64)	<0.001	1.48 (0.80 to 2.76)	0.212	0.474
60 to 69	14.31 (11.41 to 17.22)		13.06 (11.83 to 14.29)		1.08 (0.87 to 1.33)	0.497	
70 to 79	39.99 (36.43 to 43.56)		33.54 (31.91 to 35.17)		1.17 (1.07 to 1.28)	0.001	
80 to 89	107.39 (100.47 to 114.31)		92.82 (89.15 to 96.49)		1.14 (1.07 to 1.22)	<0.001	
>90	290.59 (254.66 to 326.53)		223.40 (208.92 to 237.89)		1.28 (1.12 to 1.45)	<0.001	
Gender							
Male	66.33 (62.14 to 70.52)	<0.001	54.80 (52.44 to 57.16)	<0.001	1.18 (1.11 to 1.25)	<0.001	0.452
Female	52.40 (48.08 to 56.72)		44.69 (42.66 to 46.73)		1.14 (1.06 to 1.23)	0.001	
Townsend quintile							
1(least deprived)	56.24 (50.76 to 61.72)	0.0197	48.76 (45.90 to 51.63)	<0.001	1.24 (1.13 to 1.37)	<0.001	0.323
2	59.63 (53.81 to 65.44)		48.77 (45.90 to 51.64)		1.19 (1.08 to 1.32)	0.001	
3	66.52 (59.78 to 73.25)		53.58 (50.31 to 56.85)		1.19 (1.08 to 1.32)	0.001	
4	61.20 (53.85 to 68.55)		56.57 (52.53 to 60.60)		1.04 (0.92 to 1.18)	0.497	
5(most deprived)	67.86 (57.87 to 77.85)		59.49 (54.67 to 64.31)		1.09 (0.94 to 1.26)	0.246	

PD-Parkinson's disease. *Adjusted for age, gender calendar year, social deprivation and smoking. **Wald test for categorical variable. ***Wald test for multiplicative interaction

Appendix 5-12: Figure 5-4: Association between age and unadjusted mortality rates by PD status.



Appendix 5-13: Figure 5-5: (A) Mortality rates by social deprivation adjusted for age, sex, calendar year and social deprivation. (B) Mortality rates by social deprivation adjusted for age, sex, calendar year and smoking.



Appendix 5-14: Table 5-8: Adjusted mortality rate by year from 2007 to 2016.

Year	PD cohort	Non-PD cohort	p-value
	Adjusted Mortality rate (95% CI)	Adjusted Mortality rate (95% CI)	
2007	69.47 (59.70 to 79.24)	62.91 (58.45 to 67.38)	<0.001
2008	68.18 (59.98 to 76.38)	60.00 (56.32 to 63.68)	
2009	66.91 (60.16 to 73.67)	57.23 (54.22 to 60.24)	
2010	65.67 (60.20 to 71.14)	54.58 (52.11 to 57.06)	
2011	64.45 (60.02 to 68.88)	52.06 (49.97 to 54.16)	
2012	63.25 (59.49 to 67.01)	49.65 (47.76 to 51.55)	
2013	62.08 (58.47 to 65.69)	47.36 (45.48 to 49.24)	
2014	60.92 (56.95 to 64.90)	45.17 (43.17 to 47.17)	
2015	59.79 (55.10 to 64.49)	43.08 (40.87 to 45.30)	
2016	58.68 (53.08 to 64.28)	41.09 (38.63 to 43.55)	

PD-Parkinson's disease

Appendix 6. Supplementary materials for chapter 6

Appendix 6-1. Read codes used for PD hospital admissions.

Appendix 6-1a: Read codes used to identify people with record of admissions

Read code	Hospital admission Read code description
663d.00	Emergency asthma admission since last appointment
66Ye.00	Emergency COPD admission since last appointment
66Yi.00	Multiple COPD emergency hospital admissions
8Cn..00	Admission profile form completed
8H1..00	Admit to intensive care unit
8H1..11	Admit to I.T.U.
8H11.00	Admit to cardiac ITU
8H12.00	Admit to respiratory ITU
8H13.00	Admit to neurological ITU
8H14.00	Admit to metabolic ITU
8H15.00	Admit to burns unit
8H1Z.00	Admit to intensive c.u. NOS
8H2..00	Emergency hospital admission
8H21.00	Admit medical emergency unsp.
8H22.00	Admit surgical emergency unsp.
8H23.00	Admit psychiatric emergency
8H23000	Emerg psychiatric admiss MHA
8H24.00	Admit geriatric emergency
8H28.00	Admit orthopaedic emergency
8H29.00	Admit ENT emergency
8H2A.00	Admit trauma emergency
8H2B.00	Admit ophthalmological emerg.
8H2C.00	Admit rheumatology emergency
8H2D.00	Admit dermatology emergency
8H2E.00	Admit neurology emergency
8H2F.00	Admit urology emergency
8H2G.00	Admit radiotherapy emergency
8H2H.00	Admit haematology emergency
8H2J.00	Admit diabetic emergency
8H2K.00	Admit oral surgical emergency
8H2L.00	Admit psychogeriatric emergency
8H2M.00	Admit renal medicine emergency
8H2N.00	Admit neurosurgical emergency
8H2O.00	Admit cardiothoracic emergency
8H2P.00	Emergency admission, asthma
8H2Q.00	Admit cardiology emergency
8H2R.00	Admit COPD emergency
8H2S.00	Admit heart failure emergency
8H2T.00	Emergency voluntary psychiatric admission Mental Health Act
8H2V.00	Admit ischaemic heart disease emergency
8H2W.00	Admit vascular surgery emergency
8H2X.00	Emergency hospital admission from walk-in centre
8H2Y.00	Admit anticoagulation emergency
8H2Z.00	Admit hospital emergency NOS
8H3..00	Non-urgent hospital admission
8H31.00	Non-urgent hosp.admission unsp
8H36.00	Non-urgent medical admission
8H37.00	Non-urgent surgical admission
8H39.00	Non-urgent geriatric admission

8H3E.00	Non-urgent ENT admission
8H3F.00	Non-urgent trauma admission
8H3J.00	Non-urgent neurology admission
8H3K.00	Non-urgent urology admission
8H3O.00	Non-urgent diabetic admission
8H3P.00	Non-urgent respiratory admission
8H3Q.00	Non-urgent psychogeriatric admission
8H3R.00	Non-urgent renal medicine admission
8H3S.00	Non-urgent neurosurgical admission
8H3T.00	Non-urgent cardiothoracic admission
8H3U.00	Non-urgent oral Surg.admission
8H3V.00	Non-urgent cardiological admission
8H3Z.00	Other hospital admission NOS
8Ha..00	Voluntary admission
8Hb..00	Involuntary admission
8Hd..00	Admission to hospital
8Hd0.00	Admission to community hospital
8Hd1.00	Admission by accident and emergency doctor
8Hd3.00	Admission by out of hours service doctor
8Hd5.00	Admission to acute assessment unit
8Hd6.00	Admission to stroke unit
8Hd7.00	Admission to observation ward
8Hu..00	Admission to accident and emergency department
8V0..00	Admission by doctor
8V00.00	Admission by GP
8V00000	Admission by own GP
8V00100	Admission by GP partner
8V00200	Admission by assistant GP
8V00300	Admission by associate GP
8V00400	Admission by co-op GP
8V00500	Admission by deputising GP
8V00600	Admission by GP locum
8V00700	Admission by GP registrar
8V1..00	Admission to establishment
9bK3.00	Admission notification
9Ee0F00	Admission history and physical report
ZV54015	[V]Admitted for removal of metalwork
ZV57E00	[V] Admission for toilet training
ZV60900	[V]Admission for respite care
ZV65800	[V]Admission for instruction of self catheterisation
ZV65900	[V] Admission for bladder training
ZV69.00	[V]Psychiatric patient admission details
ZV6A.00	[V]First in a series of regular day or night admissions
ZV6DA00	[V]Admitted for commencement of insulin

Appendix 6-1b: Read codes used to identify people with record of discharges

Read codes	description
8HE..00	Discharged from hospital
8HE4.00	Discharged from private hosp'l
8HE9.00	Discharged from community hospital
8HEE.00	Premature hospital discharge
93A..00	Discharge summary
9b0A.00	Discharge report
9b0B.00	Discharge summary report
9b0O.00	Initial post discharge review

9bK2.00	Discharge notification
9c0J.00	Reason for discharge
9N3D100	Hospital discharge letter received
9ND9.00	Discharge summary awaited
9NDE.00	Discharge summary awaited
9NfF.00	Key contact informed in advance of discharge
Z6N7.00	Gaining safe level of mobility prior to hospital discharge
ZLDR.00	Self-discharge
ZLDR.11	Taking own discharge
ZLE1.11	Discharge from casualty service
ZLE5111	Discharge from adult ITU service
ZLF2.00	Discharge from hospital
ZLG5.00	Discharge to sheltered housing

Appendix 6-1c: Read codes used to identify people with neuropsychiatric complications.

Read codes	**Neuropsychiatric Read code description**
1S04.00	C/O - illusions seen
1BH..11	Delusion
1BH0.00	Delusion of persecution
1BH..00	Delusions
E02z.00	Drug psychosis NOS
E021100	Drug-induced hallucinosis
1BH1.00	Grandiose delusions
146H.00	H/O: psychosis
1B1E.00	Hallucinations
Z4K3.00	Interpretation of hallucinations
225F.00	O/E - delusion of persecution
225E.00	O/E - paranoid delusions
E03y000	Organic delusional syndrome
E03y100	Organic hallucinosis syndrome
E0z..00	Organic psychoses NOS
E0...00	Organic psychotic conditions
E04..00	Other chronic organic psychoses
E02yz00	Other drug psychoses NOS
E12y.00	Other paranoid states
E12yz00	Other paranoid states NOS
E0y..00	Other specified organic psychoses
E12y000	Paranoia querulans
E12z.00	Paranoid psychosis NOS
E12..00	Paranoid states
285..11	Psychotic condition, insight present
E13z.11	Psychotic episode NOS
E00..00	Senile and presenile organic psychotic conditions
E120.00	Simple paranoid state
1B1b.00	Transient hallucinations
F481K00	Visual hallucinations
R001.00	[D]Hallucinations
R001z00	[D]Hallucinations NOS
R001000	[D]Hallucinations, auditory
R001100	[D]Hallucinations, gustatory
R001200	[D]Hallucinations, olfactory

R001300	[D]Hallucinations, tactile
R001400	[D]Visual hallucinations
Eu02z12	[X] Presenile psychosis NOS
Eu02z15	[X] Senile psychosis NOS
Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Eu23.00	[X]Acute and transient psychotic disorders
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph
Eu22111	[X]Capgras syndrome
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu22000	[X]Delusional disorder
Eu22y11	[X]Delusional dysmorphophobia
Eu22100	[X]Delusional misidentification syndrome
Eu24.00	[X]Induced delusional disorder
Eu24.12	[X]Induced paranoid disorder
Eu24.13	[X]Induced psychotic disorder
Eu05000	[X]Organic hallucinosis
Eu0z.11	[X]Organic psychosis NOS
Eu23300	[X]Other acute predominantly delusional psychotic disorders
Ryu5300	[X]Other hallucinations
Eu22y00	[X]Other persistent delusional disorders
Eu22015	[X]Paranoia
Eu22y13	[X]Paranoia querulans
Eu22011	[X]Paranoid psychosis
Eu22012	[X]Paranoid state
Eu22z00	[X]Persistent delusional disorder, unspecified
Eu22.00	[X]Persistent delusional disorders
Eu2z.11	[X]Psychosis NOS
Eu0z.12	[X]Symptomatic psychosis NOS

Appendix 6-1d: Read codes used to identify people with myocardial infarction/ischaemic heart disease

Read codes	Myocardial infarction/ischaemic heart disease Read code description
14A3.00	H/O: myocardial infarct <60
14A4.00	H/O: myocardial infarct >60
14AH.00	H/O: Myocardial infarction in last year
14AL.00	H/O: Treatment for ischaemic heart disease
14AT.00	History of myocardial infarction
322..00	ECG: myocardial ischaemia
3222.00	ECG:shows myocardial ischaemia
322Z.00	ECG: myocardial ischaemia NOS
323..00	ECG: myocardial infarction
3232.00	ECG: old myocardial infarction
3233.00	ECG: antero-septal infarct.
3234.00	ECG:posterior/inferior infarct
3235.00	ECG: subendocardial infarct
3236.00	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
792..11	Coronary artery bypass graft operations
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery

7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery
7922100	Allograft replacement of two coronary arteries
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923.00	Prosthetic replacement of coronary artery
7923.11	Prosthetic bypass of coronary artery
7923000	Prosthetic replacement of one coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924500	Revision of implantation of thoracic artery into heart
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925011	LIMA sequential anastomosis
7925012	RIMA sequential anastomosis
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925311	LIMA single anastomosis
7925312	RIMA single anastomosis
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS

7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928.00	Transluminal balloon angioplasty of coronary artery
7928.11	Percutaneous balloon coronary angioplasty
7928000	Percut transluminal balloon angioplasty one coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928300	Percut translum cutting balloon angioplasty coronary artery
7928y00	Transluminal balloon angioplasty of coronary artery OS
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929.00	Other therapeutic transluminal operations on coronary artery
7929000	Percutaneous transluminal laser coronary angioplasty
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929500	Insertion of drug-eluting coronary artery stent
7929600	Percutaneous transluminal atherectomy of coronary artery
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792A.00	Diagnostic transluminal operations on coronary artery
792Ay00	Diagnostic transluminal operation on coronary artery OS
792Az00	Diagnostic transluminal operation on coronary artery NOS
792B.00	Repair of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
793G.00	Perc translumin balloon angioplasty stenting coronary artery
793G000	Perc translum ball angio insert 1-2 drug elut stents cor art
793G100	Perc tran ball angio ins 3 or more drug elut stents cor art
793G200	Perc translum balloon angioplasty insert 1-2 stents cor art
793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC
793Gy00	OS perc translumina balloon angioplast stenting coronary art
793Gz00	Perc translum balloon angioplasty stenting coronary art NOS
793H.00	Transluminal operations on cardiac conduit
793H000	Percutaneous transluminal balloon dilation cardiac conduit
7A54500	Rotary blade angioplasty
7A6G100	Peroperative angioplasty
7A6H300	Prosthetic graft patch angioplasty
7A6H400	Percutaneous transluminal angioplasty of vascular graft
7P24000	Delivery of rehabilitation for acute cardiac disorders
8H2V.00	Admit ischaemic heart disease emergency
G3...00	Ischaemic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart

G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.12	Impending infarction
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G34..00	Other chronic ischaemic heart disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G35..00	Subsequent myocardial infarction

G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
G501.00	Post infarction pericarditis
Gyu3.00	[X]Ischaemic heart diseases
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
SP07600	Coronary artery bypass graft occlusion
ZV45700	[V]Presence of aortocoronary bypass graft
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS

Appendix 6-1e: Read codes used to identify people with chronic heart failure

Read codes	Chronic heart failure Read code description
14A6.00	H/O: heart failure
14AM.00	H/O: Heart failure in last year
1O1..00	Heart failure confirmed
2JZ..00	On optimal heart failure therapy
388D.00	New York Heart Assoc classification heart failure symptoms
585f.00	Echocardiogram shows left ventricular systolic dysfunction
585g.00	Echocardiogram shows left ventricular diastolic dysfunction
661M500	Heart failure self-management plan agreed
661N500	Heart failure self-management plan review
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
679X.00	Heart failure education
67D4.00	Heart failure information given to patient

8A54400	Monitoring of cardiac output using echocardiography
8B29.00	Cardiac failure therapy
8CeC.00	Preferred place of care for next exacerbation heart failure
8CL3.00	Heart failure care plan discussed with patient
8CMK.00	Has heart failure management plan
8CMW800	Heart failure clinical pathway
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8Hg8.00	Discharge from practice nurse heart failure clinic
8HgD.00	Discharge from heart failure nurse service
8HHb.00	Referral to heart failure nurse
8HHz.00	Referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
8HTL.00	Referral to heart failure clinic
8HTL000	Referral to rapid access heart failure clinic
8I98.00	Heart failure rehabilitation programme not available
8IB8.00	Referral to heart failure exercise programme not indicated
8IE0.00	Referral to heart failure education group declined
8IE1.00	Referral to heart failure exercise programme declined
9hH..00	Exception reporting: heart failure quality indicators
9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl
9hH1.00	Excepted heart failure quality indicators: Informed dissent
9N0k.00	Seen in heart failure clinic
9N2p.00	Seen by community heart failure nurse
9N4s.00	Did not attend practice nurse heart failure clinic
9N4w.00	Did not attend heart failure clinic
9N6T.00	Referred by heart failure nurse specialist
9Or..00	Heart failure monitoring administration
9Or0.00	Heart failure review completed
9Or1.00	Heart failure monitoring telephone invite
9Or2.00	Heart failure monitoring verbal invite
9Or3.00	Heart failure monitoring first letter
9Or4.00	Heart failure monitoring second letter
9Or5.00	Heart failure monitoring third letter
G1yz100	Rheumatic left ventricular failure
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G211000	Benign hypertensive heart disease without CCF
G211100	Benign hypertensive heart disease with CCF
G21z000	Hypertensive heart disease NOS without CCF
G21z100	Hypertensive heart disease NOS with CCF
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G400.00	Acute cor pulmonale
G41z.11	Chronic cor pulmonale
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581000	Acute left ventricular failure

G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.00	Right ventricular failure
G58z.00	Heart failure NOS
G58z.12	Cardiac failure NOS
G5y4z00	Post cardiac operation heart failure NOS
G5yy900	Left ventricular systolic dysfunction
G5yyA00	Left ventricular diastolic dysfunction
G5yyB00	Right ventricular diastolic dysfunction
G5yyE00	Right ventricular systolic dysfunction
H541000	Chronic pulmonary oedema
H584.00	Acute pulmonary oedema unspecified
H584z00	Acute pulmonary oedema NOS
SP11111	Heart failure as a complication of care
ZRad.00	New York Heart Assoc classification heart failure symptoms

Appendix 6-1f: Read codes used to identify people with stroke

Read codes	**Stroke Read code description**
1477.00	H/O: cerebrovascular disease
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
14AK.00	H/O: Stroke in last year
1M4..00	Central post-stroke pain
5C13.00	Old cerebral infarction on imaging
661M700	Stroke self-management plan agreed
661N700	Stroke self-management plan review
662e.00	Stroke/CVA annual review
662e.11	Stroke annual review
662M.00	Stroke monitoring
662M100	Stroke 6 month review
662M200	Stroke initial post discharge review
662o.00	Haemorrhagic stroke monitoring
7P24200	Delivery of rehabilitation for stroke
8HBJ.00	Stroke / transient ischaemic attack referral
8Hd6.00	Admission to stroke unit
8HHM.00	Ref to multidisciplinary stroke function improvement service
8HTQ.00	Referral to stroke clinic
8IEC.00	Ref multidisciplinary stroke function improvement declined
8OAC.00	Provision of written information about stroke
9h2..00	Exception reporting: stroke quality indicators
9h21.00	Excepted from stroke quality indicators: Patient unsuitable
9h22.00	Excepted from stroke quality indicators: Informed dissent
9N0p.00	Seen in stroke clinic
9N4X.00	DNA - Did not attend stroke clinic
F11x200	Cerebral degeneration due to cerebrovascular disease
F4K7.00	Retrobulbar haemorrhage
G6...00	Cerebrovascular disease
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage

G612.00	Basal nucleus haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G633.00	Multiple and bilateral precerebral arterial occlusion
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..11	CVA - cerebral artery occlusion
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G65..00	Transient cerebral ischaemia
G650.00	Basilar artery syndrome
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G653.00	Carotid artery syndrome hemispheric
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G67..00	Other cerebrovascular disease
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS

G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G681.00	Sequelae of intracerebral haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu6.00	[X]Cerebrovascular diseases
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6D00	[X]Sequelae/other + unspecified cerebrovascular diseases
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)

Appendix 6-1g: Read codes used to identify people with hypertension

Read codes	Hypertension Read code description
14A2.00	H/O: hypertension
6146200	Hypertension induced by oral contraceptive pill
661M600	Hypertension self-management plan agreed
661N600	Hypertension self-management plan review
662..12	Hypertension monitoring
6627.00	Good hypertension control
6628.00	Poor hypertension control
6629.00	Hypertension:follow-up default
662b.00	Moderate hypertension control
662c.00	Hypertension six month review
662d.00	Hypertension annual review
662F.00	Hypertension treatm. started
662H.00	Hypertension treatm.stopped
662O.00	On treatment for hypertension
662P.00	Hypertension monitoring
662P000	Hypertension 9 month review
662P100	Telehealth hypertension monitoring
66b2.00	Hypertension monitoring not required
67H8.00	Lifestyle advice regarding hypertension
68B1.00	Hypertension screen
68B4.00	Risk factors present at hypertension screen
7Q01.00	High cost hypertension drugs
7Q01y00	Other specified high cost hypertension drugs
7Q01z00	High cost hypertension drugs NOS
8CR4.00	Hypertension clinical management plan
8HT5.00	Referral to hypertension clinic
8I3N.00	Hypertension treatment refused

9h3..00	Exception reporting: hypertension quality indicators
9h31.00	Excepted from hypertension qual indicators: Patient unsuit
9h32.00	Excepted from hypertension qual indicators: Informed dissent
9N03.00	Seen in hypertension clinic
9N1y200	Seen in hypertension clinic
9N4L.00	DNA - Did not attend hypertension clinic
9OI..00	Hypertension monitoring admin.
9OI..11	Hypertension clinic admin.
9OI1.00	Attends hypertension monitor.
9OI2.00	Refuses hypertension monitor.
9OIA.00	Hypertension monitor.chck done
9OIA.11	Hypertension monitored
G20..00	Essential hypertension
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G22z.11	Renal hypertension
G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..11	Stage 1 hypertension
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G8y3.00	Chronic peripheral venous hypertension
Gyu2000	[X]Other secondary hypertension
Gyu2100	[X]Hypertension secondary to other renal disorders

Appendix 6-1h: Read codes used to identify people with record of falls.

Read codes	Falls Read codes description
16D..00	Falls
16D1.00	Recurrent falls
16D5.00	Fall onto outstretched hand
16D6.00	Fall
8BIG.00	Falls caused by medication
R200.12	[D] Geriatric fall
T183.00	MVTA - fall from motor vehicle while in motion
T240.00	MVNTA - fall while boarding or alighting from motor vehicle
T335.00	Fall in road vehicle NEC
T336.00	Fall on road vehicle NEC
T53..00	Fall in, on, or from aircraft
T532.00	Fall in aircraft

T533.00	Fall on aircraft
T534.00	Fall from aircraft
T53z.00	Fall in, on or from aircraft NOS
T53z000	Aircraft fall NOS - occupant of spacecraft injured
T53z300	Aircraft fall NOS - other occ comm aircraft surf/surf inj
TC...00	Accidental falls
TC...11	Fall - accidental
TC0..00	Fall on or from stairs or steps
TC00.00	Fall on or from escalator
TC00000	Fall on escalator
TC00100	Fall from escalator
TC00z00	Fall on or from escalator NOS
TC01.00	Fall on or from stairs
TC01000	Fall on stairs
TC01100	Fall from stairs
TC01z00	Fall on or from stairs NOS
TC02.00	Fall on or from steps
TC02000	Fall on steps
TC02100	Fall from steps
TC02z00	Fall on or from steps NOS
TC0z.00	Fall on or from stairs or steps NOS
TC2..00	Fall from or out of building or other structure
TC42.00	Fall from chair or bed
TC42000	Fall from chair
TC42100	Fall from bed
TC42z00	Fall from chair or bed NOS
TC5..00	Fall on same level from slipping, tripping or stumbling
TC50.00	Fall on same level from slipping
TC51.00	Fall on same level from tripping
TC52.00	Fall on same level from stumbling
TC53.00	Fall on moving sidewalk
TC5z.00	Fall on same level from slipping, tripping or stumbling NOS
TCy..00	Other falls
TCyz.00	Other accidental fall NOS
TCz..00	Accidental falls NOS
TN7..00	Injury ?accidental, fall from high place
TN70.00	Injury ?accidental, fall from residential premises
TN7z.00	Injury ?accidental, fall from high place NOS
U10..00	[X]Falls
U101.00	[X]Fall on same level from slipping, tripping and stumbling
U101000	[X]Fall same levl frm slip trip + stumb, occurrence at home
U101100	[X]Fall same level from slip trip + stumb occ resid instit
U105.00	[X]Fall involving wheelchair
U105000	[X]Fall involving wheelchair, occurrence at home
U105100	[X]Fall involvng wheelchair occurrence residential instit'n
U106.00	[X]Fall involving bed
U106000	[X]Fall involving bed, occurrence at home
U106100	[X]Fall involving bed occurrence in residential institution
U107.00	[X]Fall involving chair
U107000	[X]Fall involving chair, occurrence at home
U107100	[X]Fall involving chair occurrence in residential instit'n
U108.00	[X]Fall involving other furniture
U108000	[X]Fall involving other furniture, occurrence at home
U108100	[X]Fall involv other furniture occurrn resident institut'n
U10A.00	[X]Fall on and from stairs and steps
U10A000	[X]Fall on and from stairs and steps, occurrence at home
U10A100	[X]Fall on + from stair + step occurrnce resident instit'n
U10A511	[X]Fall on or from escalator

U10J.00	[X]Other fall on same level
U10J000	[X]Other fall on same level, occurrence at home
U10z.00	[X]Unspecified fall
U10z000	[X]Unspecified fall, occurrence at home
U10z100	[X]Unspecified fall, occurrence in residential institution
U10zy00	[X]Unspecified fall, occurrence at other specified place
U10zz00	[X]Unspecified fall, occurrence at unspecified place

Appendix 6-1i: Read codes used to identify people with fractures

Read codes	Fracture Read code descriptions
7403600	Outfracture of turbinates of nose
7403900	Surgical outfracture of turbinate of nose
7K14.00	Open surgical fracture of bone
7K14y00	Other specified open surgical fracture of bone
7K14z00	Open surgical fracture of bone NOS
7K15.00	Other surgical fracture of bone
7K15y00	Other specified other surgical fracture of bone
7K15z00	Other surgical fracture of bone NOS
B585000	Pathological fracture due to metastatic bone disease
N1y1.00	Fatigue fracture of vertebra
N1y2.00	Pars interarticularis stress fracture
N331.00	Pathological fracture
N331.13	Sponanteous fracture
N331000	Pathological fracture of thoracic vertebra
N331100	Pathological fracture of lumbar vertebra
N331700	Fracture of bone in neoplastic disease
N331C00	Pathological fracture of cervical vertebra
N331N00	Fragility fracture
N331N11	Minimal trauma fracture
N331y00	Other specified pathological fracture
N331z00	Pathological fracture NOS
NyuCE00	[X]Fracture of bone in neoplastic diseases CE
S0...00	Fracture of skull
S00..00	Fracture of vault of skull
S00..11	Frontal bone fracture
S00..12	Parietal bone fracture
S000.00	Closed fracture vault of skull without intracranial injury
S001.00	Closed fracture vault of skull with intracranial injury
S002.00	Open fracture vault of skull without intracranial injury
S003.00	Open fracture vault of skull with intracranial injury
S00z.00	Fracture of vault of skull NOS
S01..00	Fracture of base of skull
S01..11	Anterior fossa fracture
S01..12	Ethmoid sinus fracture
S01..13	Frontal sinus fracture
S01..14	Middle fossa fracture
S01..15	Occiput bone fracture
S01..16	Orbital roof fracture
S01..17	Posterior fossa fracture
S01..18	Sphenoid bone fracture
S01..19	Temporal bone fracture
S010.00	Closed fracture base of skull without intracranial injury
S011.00	Closed fracture base of skull with intracranial injury
S012.00	Open fracture base skull without mention intracranial injury
S013.00	Open fracture base of skull with intracranial injury
S01z.00	Fracture of base of skull NOS

S02..00	Fracture of face bones
S020.00	Closed fracture nose
S020.11	Closed fracture nasal bone
S021.00	Open fracture nose
S021.11	Open fracture nasal bone
S022.00	Fracture of mandible, closed
S022.11	Fracture of inferior maxilla, closed
S022.12	Fracture of lower jaw, closed
S022000	Closed fracture mandible (site unspecified)
S022100	Closed fracture of mandible, condylar process
S022200	Closed fracture of mandible, subcondylar
S022300	Closed fracture of mandible, coronoid process
S022400	Closed fracture of mandible, ramus, unspecified
S022500	Closed fracture of mandible, angle of jaw
S022600	Closed fracture of mandible, symphysis of body
S022700	Closed fracture of mandible, alveolar border of body
S022800	Closed fracture of mandible, body, other and unspecified
S022x00	Closed fracture of mandible, multiple sites
S022z00	Fracture of mandible, closed, NOS
S023.00	Fracture of mandible, open
S023.11	Fracture of lower jaw, open
S023000	Open fracture mandible (site unspecified)
S023100	Open fracture of mandible, condylar process
S023200	Open fracture of mandible, subcondylar
S023300	Open fracture of mandible, coronoid process
S023400	Open fracture of mandible, ramus, unspecified
S023500	Open fracture of mandible, angle of jaw
S023600	Open fracture of mandible, symphysis of body
S023700	Open fracture of mandible, alveolar border of body
S023800	Open fracture of mandible, body, other and unspecified
S023x00	Open fracture of mandible, multiple sites
S023z00	Fracture of mandible, open, NOS
S024.00	Fracture of malar or maxillary bones, closed
S024.11	Fracture of upper jaw, closed
S024000	Closed fracture maxilla
S024100	Closed fracture zygoma
S024z00	Fracture of malar or maxillary bones, closed, NOS
S025.00	Fracture of malar or maxillary bones, open
S025.11	Fracture of upper jaw, open
S025000	Open fracture maxilla
S025100	Open fracture zygoma
S025z00	Fracture of malar or maxillary bones, open, NOS
S026.00	Closed orbital blow-out fracture
S027.00	Open orbital blow-out fracture
S028.00	Fracture of skull and facial bones
S028000	Fracture of nasal bones
S028100	Fracture of orbital floor
S028200	Fracture of malar and maxillary bones
S028300	Fracture of mandible
S02A.00	Le Fort I fracture maxilla
S02B.00	Le Fort II fracture maxilla
S02C.00	Le Fort III fracture maxilla
S02x.00	Closed fracture other facial bone
S02x000	Fracture of alveolus, closed
S02x100	Fracture of orbit NOS, closed
S02x200	Fracture of palate, closed
S02xz00	Fracture of other facial bones, closed, NOS
S02y.00	Open fracture other facial bone

S02y000	Fracture of alveolus, open
S02y100	Fracture of orbit NOS, open
S02y200	Fracture of palate, open
S02yz00	Fracture of other facial bones,open, NOS
S02z.00	Fracture of facial bone NOS
S02z.11	Jaw fracture NOS
S03..00	Other and unqualified skull fractures
S030.00	Closed fracture of skull NOS without intracranial injury
S031.00	Closed fracture of skull NOS with intracranial injury
S033.00	Open fracture of skull NOS with intracranial injury
S03z.00	Skull fracture NOS
S03z.11	Depressed skull fracture NOS
S04..00	Multiple fractures involving skull or face with other bones
S04..11	Multiple face fractures
S04..12	Multiple skull fractures
S044.00	Multiple fractures involving skull and facial bones
S04z.00	Multiple fractures involving skull/face with other bones NOS
S0z..00	Fracture of skull NOS
S1...00	Fracture of neck and trunk
S100.00	Closed fracture of cervical spine
S100000	Closed fracture of unspecified cervical vertebra
S100100	Closed fracture atlas
S100200	Closed fracture axis
S100300	Closed fracture of third cervical vertebra
S100400	Closed fracture of fourth cervical vertebra
S100500	Closed fracture of fifth cervical vertebra
S100600	Closed fracture of sixth cervical vertebra
S100700	Closed fracture of seventh cervical vertebra
S100800	Closed fracture atlas, isolated arch or articular process
S100900	Closed fracture atlas, comminuted
S100A00	Closed fracture axis, odontoid process
S100B00	Closed fracture axis, spondylolysis
S100C00	Closed fracture axis, spinous process
S100D00	Closed fracture axis, transverse process
S100E00	Closed fracture axis, posterior arch
S100F00	Closed fracture axis, tricolumnar
S100G00	Closed fracture cervical vertebra, burst
S100H00	Closed fracture cervical vertebra, wedge
S100J00	Closed fracture cervical vertebra, spondylolysis
S100K00	Closed fracture cervical vertebra, spinous process
S100L00	Closed fracture cervical vertebra, transverse process
S100M00	Closed fracture cervical vertebra, posterior arch
S100N00	Closed fracture cervical vertebra, tricolumnar
S100x00	Multiple closed fractures of cervical vertebrae
S100z00	Closed fracture of cervical spine not otherwise specified
S101.00	Open fracture of cervical spine
S101000	Open fracture of unspecified cervical vertebra
S101100	Open fracture atlas
S101200	Open fracture axis
S101300	Open fracture of third cervical vertebra
S101400	Open fracture of fourth cervical vertebra
S101500	Open fracture of fifth cervical vertebra
S101600	Open fracture of sixth cervical vertebra
S101700	Open fracture of seventh cervical vertebra
S101800	Open fracture atlas, isolated arch or articular process
S101900	Open fracture atlas, comminuted
S101A00	Open fracture axis, odontoid process
S101B00	Open fracture axis, spondylolysis

S101C00	Open fracture axis, spinous process
S101D00	Open fracture axis, transverse process
S101E00	Open fracture axis, posterior arch
S101F00	Open fracture axis, tricolumnar
S101G00	Open fracture cervical vertebra, burst
S101H00	Open fracture cervical vertebra, wedge
S101J00	Open fracture cervical vertebra, spondylolysis
S101K00	Open fracture cervical vertebra, spinous process
S101L00	Open fracture cervical vertebra, transverse process
S101M00	Open fracture cervical vertebra, posterior arch
S101N00	Open fracture cervical vertebra, tricolumnar
S101x00	Multiple open fractures of cervical vertebrae
S101z00	Open fracture of cervical spine not otherwise specified
S102.00	Closed fracture thoracic vertebra
S102000	Closed fracture thoracic vertebra, burst
S102100	Closed fracture thoracic vertebra, wedge
S102200	Closed fracture thoracic vertebra, spondylolysis
S102300	Closed fracture thoracic vertebra, spinous process
S102400	Closed fracture thoracic vertebra, transverse process
S102500	Closed fracture thoracic vertebra, posterior arch
S102600	Closed fracture thoracic vertebra, tricolumnar
S102y00	Other specified closed fracture thoracic vertebra
S102z00	Closed fracture thoracic vertebra not otherwise specified
S103.00	Open fracture thoracic vertebra
S103000	Open fracture thoracic vertebra, burst
S103100	Open fracture thoracic vertebra, wedge
S103200	Open fracture thoracic vertebra, spondylolysis
S103300	Open fracture thoracic vertebra, spinous process
S103400	Open fracture thoracic vertebra, transverse process
S103500	Open fracture thoracic vertebra, posterior arch
S103600	Open fracture thoracic vertebra, tricolumnar
S104.00	Closed fracture lumbar vertebra
S104000	Closed fracture lumbar vertebra, burst
S104100	Closed fracture lumbar vertebra, wedge
S104200	Closed fracture lumbar vertebra, spondylolysis
S104300	Closed fracture lumbar vertebra, spinous process
S104400	Closed fracture lumbar vertebra, transverse process
S104500	Closed fracture lumbar vertebra, posterior arch
S104600	Closed fracture lumbar vertebra, tricolumnar
S105.00	Open fracture lumbar vertebra
S105000	Open fracture lumbar vertebra, burst
S105100	Open fracture lumbar vertebra, wedge
S105200	Open fracture lumbar vertebra, spondylolysis
S105300	Open fracture lumbar vertebra, spinous process
S105400	Open fracture lumbar vertebra, transverse process
S105500	Open fracture lumbar vertebra, posterior arch
S105600	Open fracture lumbar vertebra, tricolumnar
S106.00	Closed fracture sacrum
S106000	Closed compression fracture sacrum
S106100	Closed vertical fracture of sacrum
S107.00	Open fracture sacrum
S107000	Open compression fracture sacrum
S107100	Open vertical fracture of sacrum
S108.00	Closed fracture pelvis, coccyx
S109.00	Open fracture pelvis, coccyx
S10A.00	Fracture of neck
S10A000	Fracture of first cervical vertebra
S10A100	Fracture of second cervical vertebra

S10A200	Multiple fractures of cervical spine
S10B.00	Fracture of lumbar spine and pelvis
S10B000	Fracture of lumbar vertebra
S10B100	Fracture of sacrum
S10B200	Fracture of coccyx
S10B300	Fracture of ilium
S10B400	Fracture of acetabulum
S10B500	Fracture of pubis
S10B600	Multiple fractures of lumbar spine and pelvis
S10x.00	Closed fracture of spine, unspecified,
S10y.00	Open fracture of spine, unspecified,
S12..00	Fracture of rib(s), sternum, larynx and trachea
S120.00	Closed fracture rib
S120000	Closed fracture of rib, unspecified
S120100	Closed fracture of one rib
S120200	Closed fracture of two ribs
S120300	Closed fracture of three ribs
S120400	Closed fracture of four ribs
S120500	Closed fracture of five ribs
S120600	Closed fracture of six ribs
S120700	Closed fracture of seven ribs
S120800	Closed fracture of eight or more ribs
S120900	Closed fracture multiple ribs
S120A00	Cough fracture
S120z00	Closed fracture of rib(s) NOS
S121.00	Open fracture rib
S121000	Open fracture of rib, unspecified
S121100	Open fracture of one rib
S121200	Open fracture of two ribs
S121300	Open fracture of three ribs
S121400	Open fracture of four ribs
S121500	Open fracture of five ribs
S121600	Open fracture of six ribs
S121700	Open fracture of seven ribs
S121800	Open fracture of eight or more ribs
S121900	Open fracture multiple ribs
S121z00	Open fracture of rib(s) NOS
S122.00	Closed fracture sternum
S123.00	Open fracture sternum
S125.00	Closed fracture larynx and trachea
S125000	Closed fracture larynx
S125100	Closed fracture of hyoid bone
S125200	Closed fracture of thyroid cartilage
S125300	Closed fracture of trachea
S125z00	Closed fracture of larynx and trachea NOS
S126.00	Open fracture larynx and trachea
S126000	Open fracture larynx
S126100	Open fracture of hyoid bone
S126200	Open fracture of thyroid cartilage
S126300	Open fracture of trachea
S126z00	Open fracture of larynx and trachea NOS
S127.00	Fracture of rib
S127000	Multiple fractures of ribs
S127100	Cough fracture of ribs
S128.00	Fracture of sternum
S12X.00	Fracture of bony thorax, part unspecified
S12X000	Closed fracture of bony thorax part unspecified
S12X100	Open fracture of bony thorax part unspecified

S12y.00	Fracture of other parts of bony thorax
S12y000	Closed fracture of other parts of bony thorax
S12y100	Open fracture of other parts of bony thorax
S12z.00	Fracture of rib(s), sternum, larynx or trachea NOS
S12z.11	Rib fracture NOS
S12z.12	Sternum fracture NOS
S13..00	Fracture or disruption of pelvis
S130.00	Closed fracture acetabulum
S130000	Closed fracture acetabulum, anterior lip alone
S130100	Closed fracture acetabulum, posterior lip alone
S130200	Closed fracture acetabulum, anterior column
S130300	Closed fracture acetabulum, posterior column
S130400	Closed fracture acetabulum, floor
S130500	Closed fracture acetabulum, double column transverse
S130600	Closed fracture acetabulum, double column unspecified
S130y00	Other specified closed fracture acetabulum
S130z00	Closed fracture acetabulum NOS
S131.00	Open fracture acetabulum
S131000	Open fracture acetabulum, anterior lip alone
S131100	Open fracture acetabulum, posterior lip alone
S131200	Open fracture acetabulum, anterior column
S131300	Open fracture acetabulum, posterior column
S131400	Open fracture acetabulum, floor
S131500	Open fracture acetabulum, double column transverse
S131600	Open fracture acetabulum, double column unspecified
S131y00	Other specified open fracture acetabulum
S131z00	Open fracture acetabulum NOS
S132.00	Closed fracture pubis
S132000	Closed fracture pelvis, single pubic ramus
S132100	Closed fracture pelvis, multiple pubic rami - stable
S132200	Closed fracture pelvis, multiple pubic rami - unstable
S132y00	Other specified closed fracture pubis
S132z00	Closed fracture pubis NOS
S133.00	Open fracture of pubis
S133000	Open fracture pelvis, single pubic ramus
S133100	Open fracture pelvis, multiple pubic rami - stable
S133200	Open fracture pelvis, multiple pubic rami - unstable
S133y00	Other specified open fracture of pubis
S133z00	Open fracture of pubis NOS
S134.00	Other or multiple closed fracture of pelvis
S134000	Closed fracture of ilium, unspecified
S134100	Closed fracture pelvis, ischium
S134300	Closed fracture pelvis, ischial tuberosity
S134400	Closed fracture pelvis, anterior superior iliac spine
S134500	Closed fracture pelvis, anterior inferior iliac spine
S134600	Closed fracture pelvis, iliac wing
S134700	Closed vertical fracture of ilium
S134800	Closed fracture dislocation of sacro-iliac joint
S134z00	Other or multiple closed fracture of pelvis NOS
S135.00	Other or multiple open fracture of pelvis
S135000	Open fracture of ilium, unspecified
S135100	Open fracture pelvis, ischium
S135300	Open fracture pelvis, ischial tuberosity
S135400	Open fracture pelvis, anterior superior iliac spine
S135500	Open fracture pelvis, anterior inferior iliac spine
S135600	Open fracture pelvis, iliac wing
S135700	Open vertical fracture of ilium
S135800	Open fracture dislocation of sacro-iliac joint

S135y00	Other open fracture of pelvis
S135z00	Other/multiple open fracture of pelvis NOS
S13y.00	Closed fracture of pelvis NOS
S13z.00	Open fracture of pelvis NOS
S14..00	Fracture of ill-defined bones of trunk
S140.00	Closed fracture of ill-defined bone of trunk
S141.00	Open fracture of ill-defined bone of trunk
S14z.00	Fracture of ill-defined bone of trunk NOS
S15..00	Fracture of thoracic vertebra
S150.00	Multiple fractures of thoracic spine
S150000	Closed multiple fractures of thoracic spine
S150100	Open multiple fracture of thoracic spine
S1z..00	Fracture of neck and trunk NOS
S2...00	Fracture of upper limb
S2...11	Arm fracture
S20..00	Fracture of clavicle
S20..11	Collar bone fracture
S200.00	Closed fracture of clavicle
S200000	Closed fracture of clavicle, unspecified part
S200100	Closed fracture clavicle, medial end
S200200	Closed fracture clavicle, shaft
S200300	Closed fracture clavicle, lateral end
S200z00	Closed fracture of clavicle NOS
S201.00	Open fracture of clavicle
S201000	Open fracture of clavicle, unspecified part
S201100	Open fracture clavicle, medial end
S201200	Open fracture clavicle, shaft
S201300	Open fracture clavicle, lateral end
S201z00	Open fracture of clavicle NOS
S20z.00	Fracture of clavicle NOS
S21..00	Fracture of scapula
S21..11	Shoulder blade fracture
S210.00	Closed fracture of scapula
S210000	Closed fracture of scapula, unspecified part
S210100	Closed fracture scapula, acromion
S210200	Closed fracture scapula, coracoid
S210300	Closed fracture scapula, glenoid
S210400	Closed fracture scapula, blade
S210500	Closed fracture scapula, spine
S210600	Closed fracture scapula, neck
S210z00	Closed fracture of scapula NOS
S211.00	Open fracture of scapula
S211000	Open fracture of scapula, unspecified part
S211100	Open fracture scapula, acromion
S211200	Open fracture scapula, coracoid
S211300	Open fracture scapula, glenoid
S211400	Open fracture scapula, blade
S211500	Open fracture scapula, spine
S211600	Open fracture scapula, neck
S211z00	Open fracture of scapula NOS
S21z.00	Fracture of scapula NOS
S22..00	Fracture of humerus
S220.00	Closed fracture of the proximal humerus
S220000	Closed fracture of proximal humerus, unspecified part
S220100	Closed fracture proximal humerus, neck
S220200	Closed fracture of proximal humerus, anatomical neck
S220300	Closed fracture proximal humerus, greater tuberosity
S220400	Closed fracture proximal humerus, head

S220500	Closed fracture of humerus, upper epiphysis
S220600	Closed fracture proximal humerus, three part
S220700	Closed fracture proximal humerus, four part
S220z00	Closed fracture of proximal humerus not otherwise specified
S221.00	Open fracture of the proximal humerus
S221.11	Shoulder fracture - open
S221000	Open fracture of proximal humerus, unspecified part
S221100	Open fracture proximal humerus, neck
S221200	Open fracture of proximal humerus, anatomical neck
S221300	Open fracture proximal humerus, greater tuberosity
S221400	Open fracture proximal humerus, head
S221500	Open fracture of humerus, upper epiphysis
S221600	Open fracture proximal humerus, three part
S221700	Open fracture proximal humerus, four part
S221z00	Open fracture of proximal humerus not otherwise specified
S222.00	Closed fracture of humerus, shaft or unspecified part
S222000	Closed fracture of humerus NOS
S222100	Closed fracture of humerus, shaft
S222z00	Closed fracture of humerus, shaft or unspecified part NOS
S223.00	Open fracture of humerus, shaft or unspecified part
S223000	Open fracture of humerus NOS
S223100	Open fracture of humerus, shaft
S223z00	Open fracture of humerus, shaft or unspecified part NOS
S224.00	Closed fracture of the distal humerus
S224.11	Elbow fracture - closed
S224000	Closed fracture of elbow, unspecified part
S224100	Closed fracture distal humerus, supracondylar
S224200	Closed fracture distal humerus, lateral condyle
S224300	Closed fracture distal humerus, medial condyle
S224400	Closed fracture of distal humerus, condyle(s) unspecified
S224500	Closed fracture of distal humerus, trochlea
S224600	Closed fracture distal humerus, lateral epicondyle
S224700	Closed fracture distal humerus, medial epicondyle
S224800	Closed fracture distal humerus, capitellum
S224900	Closed fracture distal humerus, bicondylar (T-Y fracture)
S224x00	Closed fracture of distal humerus, multiple
S224z00	Closed fracture of distal humerus, not otherwise specified
S225.00	Open fracture of the distal humerus
S225.11	Elbow fracture - open
S225000	Open fracture of elbow, unspecified part
S225100	Open fracture distal humerus, supracondylar
S225200	Open fracture distal humerus, lateral condyle
S225300	Open fracture distal humerus, medial condyle
S225400	Open fracture of distal humerus, condyle(s) unspecified
S225500	Open fracture of distal humerus, trochlea
S225600	Open fracture distal humerus, lateral epicondyle
S225700	Open fracture distal humerus, medial epicondyle
S225800	Open fracture distal humerus, capitellum
S225900	Open fracture distal humerus, bicondylar (T-Y fracture)
S225x00	Open fracture of distal humerus, multiple
S225z00	Open fracture of distal humerus, not otherwise specified
S226.00	Fracture of upper end of humerus
S227.00	Fracture of shaft of humerus
S228.00	Fracture of lower end of humerus
S22z.00	Fracture of humerus NOS
S23..00	Fracture of radius and ulna
S23..11	Forearm fracture
S230.00	Closed fracture of proximal radius and ulna

S230000	Closed fracture of proximal forearm, unspecified part
S230100	Closed fracture olecranon, extra-articular
S230200	Closed fracture of ulna, coronoid
S230300	Closed Monteggia's fracture
S230400	Closed fracture of proximal ulna, comminuted
S230500	Closed fracture of the proximal ulna
S230600	Closed fracture radius, head
S230700	Closed fracture radius, neck
S230800	Closed fracture proximal radius, comminuted
S230900	Closed fracture of the proximal radius
S230A00	Closed fracture radius and ulna, proximal
S230B00	Closed fracture olecranon, intra-articular
S230z00	Closed fracture of proximal forearm not otherwise specified
S231.00	Open fracture of proximal radius and ulna
S231000	Open fracture of proximal forearm, unspecified
S231100	Open fracture olecranon, extra-articular
S231200	Open fracture of ulna, coronoid
S231300	Open Monteggia's fracture
S231400	Open fracture proximal ulna, comminuted
S231500	Open fracture of the proximal ulna
S231600	Open fracture radial head
S231700	Open fracture radial neck
S231800	Open fracture proximal radius, comminuted
S231900	Open fracture of the proximal radius
S231A00	Open fracture radius and ulna, proximal
S231B00	Open fracture olecranon, intra-articular
S231z00	Open fracture of forearm, upper end, NOS
S232.00	Closed fracture of radius and ulna, shaft
S232000	Closed fracture of radius, shaft, unspecified
S232100	Closed fracture of the radial shaft
S232200	Closed fracture of the ulnar shaft
S232300	Closed fracture radius and ulna, middle
S232z00	Closed fracture of radius and ulna, shaft, NOS
S233.00	Open fracture of radius and ulna, shaft
S233000	Open fracture of radius, shaft, unspecified
S233100	Open fracture of the radial shaft
S233200	Open fracture of the ulnar shaft
S233300	Open fracture radius and ulna, middle
S233z00	Open fracture of radius and ulna, shaft, NOS
S234.00	Closed fracture of radius and ulna, lower end
S234.11	Wrist fracture - closed
S234000	Closed fracture of forearm, lower end, unspecified
S234100	Closed Colles' fracture
S234111	Smith's fracture - closed
S234200	Closed fracture of the distal radius, unspecified
S234211	Dupuytren's fracture, radius - closed
S234300	Closed fracture of ulna, styloid process
S234400	Closed fracture of ulna, lower epiphysis
S234500	Closed fracture distal ulna, unspecified
S234600	Closed fracture radius and ulna, distal
S234700	Closed Smith's fracture
S234800	Closed Galeazzi fracture
S234900	Closed volar Barton's fracture
S234911	Closed volar Barton's fracture-dislocation
S234912	Closed volar Barton fracture-subluxation
S234A00	Closd dorsal Barton's fracture
S234A11	Closed dorsal Barton's fracture-dislocation
S234A12	Closed dorsal Barton fracture-subluxation

S234B00	Closed fracture radial styloid
S234C00	Closed fracture distal radius, intra-articular, die-punch
S234D00	Closed fracture distal radius, extra-articular, other type
S234E00	Closed fracture distal radius, intra-articular, other type
S234F00	Closed Barton's fracture
S234G00	Greenstick fracture of distal radius
S234z00	Closed fracture of forearm, lower end, NOS
S235.00	Open fracture of radius and ulna, lower end
S235.11	Wrist fracture - open
S235000	Open fracture of forearm, lower end, unspecified
S235100	Open Colles' fracture
S235111	Smith's fracture - open
S235200	Open fracture of the distal radius, unspecified
S235211	Dupuytren's fracture, radius - open
S235300	Open fracture of ulna, styloid process
S235400	Open fracture of ulna, lower epiphysis
S235500	Open fracture distal ulna - other
S235600	Open fracture radius and ulna, distal
S235700	Open Smith's fracture
S235800	Open Galeazzi fracture
medcode	fracturedescription
S235900	Open volar Barton's fracture
S235911	Open volar Barton fracture-dislocation
S235912	Open volar Barton fracture-subluxation
S235A00	Open dorsal Barton's fracture
S235A11	Open dorsal Barton's fracture-dislocation
S235A12	Open dorsal Barton's fracture-subluxation
S235B00	Open fracture radial styloid
S235C00	Open fracture distal radius, intra-articular, die-punch
S235D00	Open fracture distal radius, extra-articular other type
S235E00	Open fracture distal radius, intra-articular other type
S235F00	Open Barton's fracture
S235z00	Open fracture of forearm, lower end, NOS
S236.00	Fracture of upper end of ulna
S237.00	Fracture of upper end of radius
S238.00	Fracture of shaft of ulna
S239.00	Fracture of shaft of radius
S23A.00	Fracture of shafts of both ulna and radius
S23B.00	Fracture of lower end of radius
S23C.00	Fracture of lower end of both ulna and radius
S23x.00	Closed fracture of radius and ulna, unspecified part
S23x000	Closed fracture of forearm, unspecified
S23x100	Closed fracture of radius (alone), unspecified
S23x111	Fracture of radius NOS
S23x200	Closed fracture of ulna (alone), unspecified
S23x211	Fracture of ulna NOS
S23x300	Closed fracture of the radius and ulna
S23xz00	Closed fracture of radius and ulna, NOS
S23y.00	Open fracture of radius and ulna, unspecified part
S23y000	Open fracture of forearm, unspecified
S23y100	Open fracture of radius (alone), unspecified
S23y200	Open fracture of ulna (alone), unspecified
S23y300	Open fracture of the radius and ulna
S23yz00	Open fracture of radius and ulna, NOS
S23z.00	Fracture of radius and ulna, NOS
S24..00	Fracture of carpal bone
S24..11	Hand fracture - carpal bone
S240.00	Closed fracture of carpal bone

S240000	Closed fracture of carpal bone, unspecified
S240100	Closed fracture of the scaphoid
S240200	Closed fracture lunate
S240300	Closed fracture triquetral
S240400	Closed fracture pisiform
S240500	Closed fracture trapezium
S240600	Closed fracture trapezoid
S240700	Closed fracture capitate
S240800	Closed fracture hamate
S240900	Closed fracture hamate, hook
S240A00	Closed fracture scaphoid, proximal pole
S240B00	Closed fracture scaphoid, waist, transverse
S240C00	Closed fracture scaphoid, waist, oblique
S240D00	Closed fracture scaphoid, waist, comminuted
S240E00	Closed fracture scaphoid, tuberosity
S240F00	Closed fracture carpal bones, multiple
S240y00	Closed fracture of other carpal bone
S240z00	Closed fracture of carpal bone NOS
S241.00	Open fracture of carpal bone
S241000	Open fracture of carpal bone, unspecified
S241100	Open fracture of the scaphoid
S241200	Open fracture lunate
S241300	Open fracture triquetral
S241400	Open fracture pisiform
S241500	Open fracture trapezium
S241600	Open fracture trapezoid
S241700	Open fracture capitate
S241800	Open fracture hamate
S241900	Open fracture hamate, hook
S241A00	Open fracture scaphoid, proximal pole
S241B00	Open fracture scaphoid, waist, transverse
S241C00	Open fracture scaphoid, waist, oblique
S241D00	Open fracture scaphoid, waist, comminuted
S241E00	Open fracture scaphoid, tuberosity
S241F00	Open fracture carpal bones, multiple
S241y00	Open fracture of other carpal bone
S241z00	Open fracture of carpal bone NOS
S242.00	Fracture at wrist and hand level
S242000	Fracture of scaphoid
S242100	Fracture of first metacarpal bone
S242200	Fracture of other metacarpal bone
S242300	Multiple fractures of metacarpal bones
S24z.00	Fracture of carpal bone NOS
S25..00	Fracture of metacarpal bone
S25..11	Hand fracture - metacarpal bone
S250.00	Closed fracture of metacarpal bone(s)
S250000	Closed fracture of metacarpal bone (s), site unspecified
S250200	Closed fracture finger metacarpal base
S250300	Closed fracture finger metacarpal shaft
S250400	Closed fracture finger metacarpal neck
S250500	Closed fracture finger metacarpal head
S250600	Closed fracture finger metacarpal
S250700	Closed fracture finger metacarpal, multiple
S250800	Closed fracture of thumb metacarpal
S250A00	Closed fracture thumb metacarpal shaft
S250B00	Closed fracture thumb metacarpal neck
S250C00	Closed fracture thumb metacarpal head
S250x00	Closed fractures of multiple sites of unspecified metacarpus

S250z00	Closed fracture of metacarpal bone(s) NOS
S251.00	Open fracture of metacarpal bone(s)
S251000	Open fracture of metacarpal bone(s), site unspecified
S251200	Open fracture finger metacarpal base
S251300	Open fracture finger metacarpal shaft
S251400	Open fracture finger metacarpal neck
S251500	Open fracture finger metacarpal head
S251600	Open fracture finger metacarpal
S251700	Open fracture finger metacarpal, multiple
S251800	Open fracture of thumb metacarpal
S251A00	Open fracture thumb metacarpal shaft
S251B00	Open fracture thumb metacarpal neck
S251C00	Open fracture thumb metacarpal head
S251x00	Open fractures of multiple sites of unspecified metacarpus
S251z00	Open fracture of metacarpal bone(s) NOS
S252.00	Closed fracture sesamoid bone of hand
S253.00	Open fracture sesamoid bone of hand
S26..00	Fracture of one or more phalanges of hand
S26..11	Finger fracture
S26..12	Thumb fracture excluding base
S260.00	Closed fracture of one or more phalanges of hand
S260000	Closed fracture of phalanx or phalanges, unspecified
S260300	Closed fracture thumb proximal phalanx
S260400	Closed fracture thumb proximal phalanx, base
S260500	Closed fracture thumb proximal phalanx, shaft
S260600	Closed fracture thumb proximal phalanx, neck
S260700	Closed fracture thumb proximal phalanx, head
S260800	Closed fracture thumb distal phalanx
S260900	Closed fracture thumb distal phalanx, base
S260A00	Closed fracture thumb distal phalanx, shaft
S260B00	Closed fracture thumb distal phalanx, tuft
S260C00	Closed fracture thumb distal phalanx, mallet
S260D00	Closed fracture finger proximal phalanx
S260E00	Closed fracture finger proximal phalanx, base
S260F00	Closed fracture finger proximal phalanx, shaft
S260G00	Closed fracture finger proximal phalanx, neck
S260H00	Closed fracture finger proximal phalanx, head
S260J00	Closed fracture finger proximal phalanx, multiple
S260K00	Closed fracture finger middle phalanx
S260L00	Closed fracture finger middle phalanx, base
S260M00	Closed fracture finger middle phalanx, shaft
S260N00	Closed fracture finger middle phalanx, neck
S260P00	Closed fracture finger middle phalanx, head
S260Q00	Closed fracture finger middle phalanx, multiple
S260R00	Closed fracture finger distal phalanx
S260S00	Closed fracture finger distal phalanx, base
S260T00	Closed fracture finger distal phalanx, shaft
S260U00	Closed fracture finger distal phalanx, tuft
S260V00	Closed fracture finger distal phalanx, mallet
S260W00	Closed fracture finger distal phalanx, multiple
S260x00	Closed fractures of phalanx or phalanges, multiple sites
S260z00	Closed fracture of one or more phalanges of hand NOS
S261.00	Open fracture of one or more phalanges of hand
S261000	Open fracture of phalanx or phalanges, unspecified
S261300	Open fracture thumb proximal phalanx
S261400	Open fracture thumb proximal phalanx, base
S261500	Open fracture thumb proximal phalanx, shaft
S261600	Open fracture thumb proximal phalanx, neck

S261700	Open fracture thumb proximal phalanx, head
S261800	Open fracture thumb distal phalanx
S261900	Open fracture thumb distal phalanx, base
S261A00	Open fracture thumb distal phalanx, shaft
S261B00	Open fracture thumb distal phalanx, tuft
S261C00	Open fracture thumb distal phalanx, mallet
S261D00	Open fracture finger proximal phalanx
S261E00	Open fracture finger proximal phalanx, base
S261F00	Open fracture finger proximal phalanx, shaft
S261G00	Open fracture finger proximal phalanx, neck
S261H00	Open fracture finger proximal phalanx, head
S261J00	Open fracture finger proximal phalanx, multiple
S261K00	Open fracture finger middle phalanx
S261L00	Open fracture finger middle phalanx, base
S261M00	Open fracture finger middle phalanx, shaft
S261N00	Open fracture finger middle phalanx, neck
S261P00	Open fracture finger middle phalanx, head
S261Q00	Open fracture finger middle phalanx, multiple
S261R00	Open fracture finger distal phalanx
S261S00	Open fracture finger distal phalanx, base
S261T00	Open fracture finger distal phalanx, shaft
S261U00	Open fracture finger distal phalanx, tuft
S261V00	Open fracture finger distal phalanx, mallet
S261W00	Open fracture finger distal phalanx, multiple
S261x00	Open fracture of phalanx or phalanges, multiple sites
S261z00	Open fracture of one or more phalanges of hand NOS
S262.00	Fracture of thumb
S263.00	Fracture of other finger
S264.00	Multiple fractures of fingers
S26z.00	Fracture of one or more phalanges of hand NOS
S27..00	Multiple fractures of hand bones
S270.00	Closed multiple fractures of hand bones
S271.00	Open multiple fractures of hand bones
S27z.00	Multiple fractures of hand bones NOS
S28..00	Ill-defined fractures of upper limb
S28..11	Ill-defined fracture of arm
S280.00	Closed ill-defined fractures of upper limb
S281.00	Open ill-defined fractures of upper limb
S28z.00	Ill-defined fractures of upper limb NOS
S29..11	Multiple fractures of arm
S29..12	Multiple rib fractures
S29..13	Multiple fractures of sternum
S292.00	Multiple fractures of clavicle, scapula and humerus
S292000	Closed multiple fractures of clavicle, scapula and humerus
S292100	Open multiple fractures of clavicle, scapula and humerus
S293.00	Multiple fractures of forearm
S294.00	Fractures involving multiple regions of both upper limbs
S294000	Cl fractures involving multiple regions of both upper limbs
S294100	Op fractures involving multiple regions of both upper limbs
S2A..00	Fracture of upper limb, level unspecified
S2B..00	Fracture of bone of hand
S2z..00	Fracture of upper limb NOS
S3...00	Fracture of lower limb
S3...11	Leg fracture
S30..00	Fracture of neck of femur
S30..11	Hip fracture
S300.00	Closed fracture proximal femur, transcervical
S300100	Closed fracture proximal femur, transepiphyseal

S300200	Closed fracture proximal femur, midcervical section
S300300	Closed fracture proximal femur, basicervical
S300311	Closed fracture, base of neck of femur
S300400	Closed fracture head of femur
S300600	Closed fracture proximal femur, subcapital, Garden grade I
S300700	Closed fracture proximal femur, subcapital, Garden grade II
S300800	Closed fracture proximal femur, subcapital, Garden grade III
S300900	Closed fracture proximal femur, subcapital, Garden grade IV
S300A00	Closed fracture of femur, upper epiphysis
S300y00	Closed fracture proximal femur, other transcervical
S300y11	Closed fracture of femur, subcapital
S300z00	Closed fracture proximal femur, transcervical, NOS
S301.00	Open fracture proximal femur, transcervical
S301100	Open fracture proximal femur, transepiphyseal
S301200	Open fracture proximal femur, midcervical section
S301300	Open fracture proximal femur, basicervical
S301311	Open fracture base of neck of femur
S301400	Open fracture head, femur
S301500	Open fracture proximal femur,subcapital, Garden grade unspec
S301600	Open fracture proximal femur,subcapital, Garden grade I
S301700	Open fracture proximal femur,subcapital, Garden grade II
S301800	Open fracture proximal femur,subcapital, Garden grade III
S301900	Open fracture proximal femur,subcapital, Garden grade IV
S301A00	Open fracture of femur, upper epiphysis
S301y00	Open fracture proximal femur, other transcervical
S301y11	Open fracture of femur, subcapital
S301z00	Open fracture proximal femur, transcervical, NOS
S302.00	Closed fracture of proximal femur, pertrochanteric
S302011	Closed fracture of femur, greater trochanter
S302012	Closed fracture of femur, lesser trochanter
S302100	Closed fracture proximal femur, intertrochanteric, two part
S302200	Closed fracture proximal femur, subtrochanteric
S302400	Closed fracture of femur, intertrochanteric
S303.00	Open fracture of proximal femur, pertrochanteric
S303011	Open fracture of femur, greater trochanter
S303012	Open fracture of femur, lesser trochanter
S303100	Open fracture proximal femur, intertrochanteric, two part
S303200	Open fracture proximal femur, subtrochanteric
S303300	Open fracture proximal femur, intertrochanteric, comminuted
S303400	Open fracture of femur, intertrochanteric
S303z00	Open fracture of proximal femur, pertrochanteric, NOS
S304.00	Pertrochanteric fracture
S305.00	Subtrochanteric fracture
S30w.00	Closed fracture of unspecified proximal femur
S30x.00	Open fracture of unspecified proximal femur
S30y.00	Closed fracture of neck of femur NOS
S30y.11	Hip fracture NOS
S30z.00	Open fracture of neck of femur NOS
S31..00	Other fracture of femur
S310.00	Closed fracture of femur, shaft or unspecified part
S310000	Closed fracture of femur, unspecified part
S310011	Thigh fracture NOS
S310012	Upper leg fracture NOS
S310100	Closed fracture shaft of femur
S310z00	Closed fracture of shaft or unspecified part, NOS
S311.00	Open fracture of femur, shaft or unspecified part
S311000	Open fracture of femur, unspecified part
S311100	Open fracture shaft of femur

S311z00	Open fracture of femur, shaft or unspecified part, NOS
S312.00	Closed fracture distal femur
S312.11	Closed fracture of femur, distal end
S312000	Closed fracture of distal femur, unspecified
S312100	Closed fracture of femoral condyle, unspecified
S312200	Closed fracture of femur, lower epiphysis
S312300	Closed fracture distal femur, supracondylar
S312400	Closed fracture distal femur, medial condyle
S312500	Closed fracture distal femur, lateral condyle
S312600	Closed fracture distal femur, bicondylar (T-Y fracture)
S312x00	Closed fracture distal femur, comminuted/intra-articular
S312z00	Closed fracture of distal femur not otherwise specified
S313.00	Open fracture distal femur
S313.11	Open fracture of femur, distal end
S313000	Open fracture distal femur, unspecified
S313100	Open fracture of femoral condyle, unspecified
S313200	Open fracture of femur, lower epiphysis
S313300	Open fracture distal femur, supracondylar
S313400	Open fracture distal femur, medial condyle
S313500	Open fracture distal femur, lateral condyle
S313600	Open fracture distal femur, bicondylar (T-Y fracture)
S313x00	Open fracture distal femur, comminuted/intra-articular
S313z00	Open fracture of distal femur not otherwise specified
S314.00	Fracture of shaft of femur
S315.00	Fracture of lower end of femur
S31z.00	Fracture of femur, NOS
S32..00	Fracture of patella
S320.00	Closed fracture of the patella
S320000	Closed fracture patella, transverse
S320100	Closed fracture patella, proximal pole
S320200	Closed fracture patella, distal pole
S320300	Closed fracture patella, vertical
S320400	Closed fracture patella, comminuted (stellate)
S321.00	Open fracture of the patella
S321000	Open fracture patella, transverse
S321100	Open fracture patella, proximal pole
S321200	Open fracture patella, distal pole
S321300	Open fracture patella, vertical
S321400	Open fracture patella, comminuted (stellate)
S32z.00	Fracture of patella, NOS
S33..00	Fracture of tibia and fibula
S330.00	Closed fracture of tibia and fibula, proximal
S330000	Closed fracture of the proximal tibia
S330011	Closed fracture of tibial condyles
S330012	Closed fracture of tibial tuberosity
S330100	Closed fracture proximal fibula
S330200	Closed fracture of tibia and fibula, proximal
S330300	Closed fracture proximal tibia, medial condyle (plateau)
S330400	Closed fracture proximal tibia, lateral condyle (plateau)
S330500	Closed fracture proximal tibia, bicondylar
S330600	Closed fracture spine, tibia
S330700	Closed fracture tubercle, tibia
S330800	Closed fracture fibula, head
S330900	Closed fracture fibula, neck
S330z00	Closed fracture of tibia and fibula, proximal NOS
S331.00	Open fracture of tibia and fibula, proximal
S331000	Open fracture of the proximal tibia
S331011	Open fracture of tibial condyles

S331012	Open fracture of tibial tuberosity
S331100	Open fracture proximal fibula
S331200	Open fracture of tibia and fibula, proximal
S331300	Open fracture proximal tibia, medial condyle (plateau)
S331400	Open fracture proximal tibia, lateral condyle (plateau)
S331500	Open fracture proximal tibia, bicondylar
S331600	Open fracture spine, tibia
S331700	Open fracture tubercle, tibia
S331800	Open fracture fibula, head
S331900	Open fracture fibula, neck
S331A00	Open fracture tibial plateau
S331z00	Open fracture of tibia and fibula, proximal NOS
S332.00	Closed fracture of tibia/fibula, shaft
S332000	Closed fracture shaft of tibia
S332100	Closed fracture shaft of fibula
S332200	Closed fracture of tibia and fibula, shaft
S332z00	Closed fracture of tibia and fibula, shaft, NOS
S333.00	Open fracture of tibia/fibula, shaft
S333000	Open fracture shaft of tibia
S333100	Open fracture shaft of fibula
S333200	Open fracture of tibia and fibula, shaft
S333z00	Open fracture of tibia and fibula, shaft, NOS
S334.00	Closed fracture distal tibia
S334000	Closed fracture distal tibia, extra-articular
S334100	Closed fracture distal tibia, intra-articular
S335.00	Open fracture distal tibia
S335000	Open fracture distal tibia, extra-articular
S335100	Open fracture distal tibia, intra-articular
S336.00	Fracture of upper end of tibia
S336000	Fracture tibial plateau
S337.00	Fracture of shaft of tibia
S338.00	Fracture of lower end of tibia
S339.00	Fracture of fibula alone
S339000	Closed fracture of distal fibula
S339100	Open fracture of distal fibula
S33A.00	Fracture of tibia
S33B.00	Open fracture of distal tibia and fibula
S33C.00	Closed fracture of distal tibia and fibula
S33x.00	Closed fracture of tibia and fibula, unspecified part, NOS
S33x.11	Lower leg fracture NOS
S33x000	Closed fracture of tibia, unspecified part, NOS
S33x100	Closed fracture of fibula, unspecified part, NOS
S33x200	Closed fracture of tibia and fibula, unspecified part
S33xz00	Closed fracture of tibia and fibula, unspecified part, NOS
S33y.00	Open fracture of tibia and fibula, unspecified part, NOS
S33y000	Open fracture of tibia, unspecified part, NOS
S33y100	Open fracture of fibula, unspecified part, NOS
S33y200	Open fracture of tibia and fibula, unspecified part
S33yz00	Open fracture of tibia and fibula, unspecified part, NOS
S33z.00	Fracture of tibia and fibula, NOS
S34..00	Fracture of ankle
S340.00	Closed fracture ankle, medial malleolus
S341.00	Open fracture ankle, medial malleolus
S342.00	Closed fracture ankle, lateral malleolus
S342000	Closed fracture ankle, lateral malleolus, low
S342100	Closed fracture ankle, lateral malleolus, high
S343.00	Open fracture ankle, lateral malleolus
S343000	Open fracture ankle, lateral malleolus, low

S343100	Open fracture ankle, lateral malleolus, high
S344.00	Closed fracture ankle, bimalleolar
S344.11	Dupuytren's fracture, fibula
S344.12	Pott's fracture - ankle
S344000	Closed fracture ankle, bimalleolar, low fibular fracture
S344100	Closed fracture ankle, bimalleolar, high fibular fracture
S345.00	Open fracture ankle, bimalleolar
S345000	Open fracture ankle, bimalleolar, low fibular fracture
S345100	Open fracture ankle, bimalleolar, high fibular fracture
S346.00	Closed fracture ankle, trimalleolar
S346000	Closed fracture ankle, trimalleolar, low fibular fracture
S346100	Closed fracture ankle, trimalleolar, high fibular fracture
S347.00	Open fracture ankle, trimalleolar
S347000	Open fracture ankle, trimalleolar, low fibular fracture
S347100	Open fracture ankle, trimalleolar, high fibular fracture
S348.00	Fracture of medial malleolus
S349.00	Fracture of lateral malleolus
S34x.00	Closed fracture ankle, unspecified
S34y.00	Open fracture ankle, unspecified
S34z.00	Fracture of ankle, NOS
S35..00	Fracture of one or more tarsal and metatarsal bones
S35..11	Metatarsal bone fracture
S35..12	Tarsal bone fracture
S350.00	Closed fracture of calcaneus
S350.11	Heel bone fracture
S350.12	Os calcis fracture
S350000	Closed fracture calcaneus, extra-articular
S350100	Closed fracture calcaneus, intra-articular
S351.00	Open fracture of calcaneus
S351000	Open fractures calcaneus, extra-articular
S351100	Open fractures calcaneus, intra-articular
S352.00	Closed fracture of other tarsal and metatarsal bones
S352.11	March fracture
S352000	Closed fracture of tarsal bone, unspecified
S352100	Closed fracture of talus
S352111	Closed fracture of astragalus
S352200	Closed fracture navicular
S352300	Closed fracture cuboid
S352400	Closed fracture medial cuneiform
S352500	Closed fracture intermediate cuneiform
S352600	Closed fracture lateral cuneiform
S352700	Closed fracture metatarsal
S352800	Closed fracture talus, head
S352900	Closed fracture talus, neck
S352A00	Closed fracture talus, body
S352B00	Closed fracture metatarsal base
S352C00	Closed fracture metatarsal shaft
S352D00	Closed fracture metatarsal neck
S352E00	Closed fracture metatarsal head
S352F00	Closed fracture metatarsal, multiple
S352G00	Closed tarsal fractures, multiple
S352H00	Closed fracture of cuneiforms
S352J00	Closed fracture of base of fifth metatarsal
S352z00	Closed fracture of one or more tarsal + metatarsal bones NOS
S353.00	Open fracture of other tarsal and metatarsal bones
S353000	Open fracture of tarsal bone, unspecified
S353100	Open fracture of talus
S353111	Open fracture of astragalus

S353200	Open fracture navicular
S353300	Open fracture cuboid
S353400	Open fracture medial cuneiform
S353500	Open fracture intermediate cuneiform
S353600	Open fracture lateral cuneiform
S353700	Open fracture metatarsal
S353800	Open fracture talus, head
S353900	Open fracture talus, neck
S353A00	Open fracture talus, body
S353B00	Open fracture metatarsal base
S353C00	Open fracture metatarsal shaft
S353D00	Open fracture metatarsal neck
S353E00	Open fracture metatarsal head
S353F00	Open fracture metatarsal, multiple
S353G00	Open tarsal fractures, multiple
S353H00	Open fracture cuneiforms
S353J00	Open fracture of base of fifth metatarsal
S353z00	Open fracture of tarsal and metatarsal bones NOS
S354.00	Fracture of calcaneus
S355.00	Fracture of talus
S356.00	Fracture of metatarsal bone
S35z.00	Fracture of tarsal and metatarsal bones NOS
S36..00	Fracture of one or more phalanges of foot
S36..11	Toe fracture
S360.00	Closed fracture of one or more phalanges of foot
S360000	Closed fracture proximal phalanx, toe
S360100	Closed fracture middle phalanx, toe
S360200	Closed fracture distal phalanx, toe
S360300	Closed fracture multiple phalanges, toe
S361.00	Open fracture of one or more phalanges of foot
S361000	Open fracture proximal phalanx, toe
S361100	Open fracture middle phalanx, toe
S361200	Open fracture distal phalanx, toe
S361300	Open fracture multiple phalanges, toe
S362.00	Fracture of great toe
S362000	Closed fracture of great toe
S362100	Open fracture of great toe
S363.00	Fracture of other toe
S36z.00	Fracture of one or more phalanges of foot NOS
S37..00	Fracture of lower limb, level unspecified
S370.00	Closed fracture of lower limb, level unspecified
S371.00	Open fracture of lower limb, level unspecified
medcode	fracturedescription
S3X..00	Fracture of lower leg, part unspecified
S3x..00	Other, multiple and ill-defined fractures of lower limb
S3x0.00	Other, multiple and ill-defined closed fractures lower limb
S3x1.00	Other, multiple and ill-defined open fractures of lower limb
S3x2.00	Multiple fractures of femur
S3x3.00	Multiple fractures of lower leg
S3x4.00	Multiple fractures of foot
S3xz.00	Other, multiple and ill-defined fractures of lower limb NOS
S3z..00	Fracture of unspecified bones
S3z..11	Fracture NOS
S3z0.00	Closed fracture of bones, unspecified
S3z0000	Greenstick fracture
S3z1.00	Open fracture of bones, unspecified
S3z2.00	Stress fracture
S3zz.00	Fracture of bones NOS

S4...13	Fracture dislocations and fracture subluxations
S4A..00	Fracture-dislocation or subluxation shoulder
S4A0.00	Closed fracture-dislocation shoulder
S4A0000	Closed fracture-dislocation shoulder joint
S4A0100	Closed fracture-dislocation acromio-clavicular joint
S4A1.00	Open fracture-dislocation shoulder
S4A1000	Open fracture-dislocation shoulder joint
S4A1100	Open fracture-dislocation acromio-clavicular joint
S4A2.00	Closed fracture-subluxation shoulder
S4A2000	Closed fracture-subluxation shoulder joint
S4A2100	Closed fracture-subluxation acromio-clavicular joint
S4A3.00	Open fracture-subluxation shoulder
S4A3000	Open fracture-subluxation shoulder joint
S4A3100	Open fracture-subluxation acromio-clavicular joint
S4B..00	Fracture-dislocation or subluxation elbow
S4B0.00	Closed fracture-dislocation elbow
S4B0000	Closed fracture-dislocation elbow joint
S4B0100	Closed fracture-dislocation superior radio-ulnar joint
S4B1.00	Open fracture-dislocation elbow
S4B1000	Open fracture-dislocation elbow joint
S4B1100	Open fracture-dislocation superior radio-ulnar joint
S4B2.00	Closed fracture-subluxation elbow
S4B2000	Closed fracture-subluxation elbow joint
S4B2100	Closed fracture-subluxation superior radio-ulnar joint
S4B3.00	Open fracture-subluxation elbow
S4B3000	Open fracture-subluxation elbow joint
S4B3100	Open fracture-subluxation superior radio-ulnar joint
S4C..00	Fracture-dislocation or subluxation of wrist
S4C0.00	Closed fracture dislocation of wrist
S4C0000	Closed fracture-dislocation distal radio-ulnar joint
S4C0100	Closed fracture-dislocation radiocarpal joint
S4C0200	Closed fracture-dislocation mid carpal
S4C0300	Closed fracture-dislocation, carpometacarpal joint
S4C0400	Closed fracture-dislocation lunate (volar)
S4C0500	Closed fracture-dislocation peri-lunate (dorsal)
S4C0600	Closed fracture-dislocation peri-lunate trans-scaphoid
S4C0y00	Closed fracture-dislocation other carpal
S4C1.00	Open fracture dislocation wrist
S4C1000	Open fracture-dislocation, distal radio-ulnar joint
S4C1100	Open fracture-dislocation radiocarpal joint
S4C1200	Open fracture-dislocation mid carpal
S4C1300	Open fracture-dislocation carpometacarpal joint
S4C1400	Open fracture-dislocation lunate (volar)
S4C1500	Open fracture-dislocation peri-lunate (dorsal)
S4C1600	Open fracture-dislocation peri-lunate trans-scaphoid
S4C1y00	Open fracture-dislocation other carpal
S4C2.00	Closed fracture-subluxation of the wrist
S4C2000	Closed fracture-subluxation, distal radio-ulnar jt
S4C2100	Closed fracture-subluxation radiocarpal joint
S4C2200	Closed fracture-subluxation mid carpal
S4C2300	Closed fracture-subluxation, carpometacarpal joint
S4C2400	Closed fracture-subluxation lunate (volar)
S4C2500	Closed fracture-subluxation peri-lunate (dorsal)
S4C2600	Closed fracture-subluxation peri-lunate trans-scaphoid
S4C2y00	Closed fracture-subluxation other carpal
S4C3.00	Open fracture-subluxation of the wrist
S4C3000	Open fracture-subluxation, distal radio-ulnar joint
S4C3100	Open fracture-subluxation radiocarpal joint

S4C3200	Open fracture-subluxation mid carpal
S4C3300	Open fracture-subluxation, carpometacarpal joint
S4C3400	Open fracture-subluxation lunate (volar)
S4C3500	Open fracture-subluxation peri-lunate (dorsal)
S4C3600	Open fracture-subluxation peri-lunate trans-scaphoid
S4C3y00	Open fracture-subluxation other carpal
S4D..00	Fracture-dislocation/subluxation finger/thumb
S4D0.00	Closed fracture-dislocation digit
S4D0000	Closed fracture-dislocation digit, unspecified
S4D0100	Closed fracture-dislocation, metacarpophalangeal joint
S4D0200	Closed fracture-dislocation IPJ, unspecified
S4D0300	Closed fracture-dislocation, distal interphalangeal joint
S4D0400	Closed fracture-dislocation, proximal interphalangeal joint
S4D0500	Closed fracture-dislocation, interphalangeal joint thumb
S4D0600	Closed fracture-dislocation multiple digits
S4D1.00	Open fracture-dislocation digit
S4D1000	Open fracture-dislocation digit, unspecified
S4D1100	Open fracture-dislocation, metacarpophalangeal joint
S4D1200	Open fracture-dislocation IPJ, unspecified
S4D1300	Open fracture-dislocation, distal interphalangeal joint
S4D1400	Open fracture-dislocation, proximal interphalangeal joint
S4D1500	Open fracture-dislocation, interphalangeal joint thumb
S4D1600	Open fracture-dislocation multiple digits
S4D2.00	Closed fracture-subluxation digit
S4D2000	Closed fracture-subluxation digit, unspecified
S4D2100	Closed fracture-subluxation, metacarpophalangeal joint
S4D2200	Closed fracture-subluxation IPJ, unspecified
S4D2300	Closed fracture-subluxation, distal interphalangeal joint
S4D2400	Closed fracture-subluxation, proximal interphalangeal joint
S4D2500	Closed fracture-subluxation, interphalangeal joint thumb
S4D2600	Closed fracture-subluxation multiple digits
S4D3.00	Open fracture-subluxation digit
S4D3000	Open fracture-subluxation digit, unspecified
S4D3100	Open fracture-subluxation, metacarpophalangeal joint
S4D3200	Open fracture-subluxation IPJ, unspecified
S4D3300	Open fracture-subluxation, distal interphalangeal joint
S4D3400	Open fracture-subluxation, proximal interphalangeal joint
S4D3500	Open fracture-subluxation, interphalangeal joint thumb
S4D3600	Open fracture-subluxation multiple digits
S4E..00	Fracture-dislocation or subluxation hip
S4E0.00	Closed fracture-dislocation, hip joint
S4E1.00	Open fracture-dislocation, hip joint
S4E2.00	Closed fracture-subluxation, hip joint
S4E3.00	Open fracture-subluxation, hip joint
S4F..00	Fracture-dislocation or subluxation knee
S4F0.00	Closed fracture-dislocation, knee joint
S4F1.00	Open fracture-dislocation, knee joint
S4F2.00	Closed fracture-subluxation, knee joint
S4F3.00	Open fracture-subluxation, knee joint
S4F4.00	Closed fracture-dislocation, patello-femoral joint
S4F5.00	Open fracture-dislocation, patello-femoral joint
S4F6.00	Closed fracture-subluxation, patello-femoral joint
S4F7.00	Open fracture-subluxation, patello-femoral joint
S4G..00	Fracture-dislocation or subluxation ankle
S4G0.00	Closed fracture-dislocation, ankle joint
S4G1.00	Open fracture-dislocation, ankle joint
S4G2.00	Closed fracture-subluxation, ankle joint
S4G3.00	Open fracture-subluxation, ankle joint

S4H..00	Fracture-dislocation or subluxation foot
S4H0.00	Closed fracture-dislocation foot
S4H0000	Closed fracture-dislocation, subtalar joint
S4H0100	Closed fracture-dislocation, midtarsal joint
S4H0200	Closed fracture-dislocation, tarsometatarsal joint
S4H0400	Closed fracture-dislocation, IPJ, single toe
S4H0600	Closed fracture-dislocation, IPJ, multiple toes
S4H1.00	Open fracture-dislocation, foot
S4H1000	Open fracture-dislocation, subtalar joint
S4H1100	Open fracture-dislocation, midtarsal joint
S4H1200	Open fracture-dislocation, tarsometatarsal joint
S4H1300	Open fracture-dislocation, metatarsophalangeal joint, single
S4H1400	Open fracture-dislocation, IPJ, single toe
S4H1600	Open fracture-dislocation, IPJ, multiple toes
S4H2.00	Closed fracture-subluxation, foot
S4H2000	Closed fracture-subluxation, subtalar joint
S4H2100	Closed fracture-subluxation, midtarsal joint
S4H2200	Closed fracture-subluxation, tarsometatarsal joint
S4H2400	Closed fracture-subluxation, IPJ, single toe
S4H2600	Closed fracture-subluxation, IPJ, multiple toes
S4H3.00	Open fracture-subluxation, foot
S4H3000	Open fracture-subluxation, subtalar joint
S4H3100	Open fracture-subluxation, midtarsal joint
S4H3200	Open fracture-subluxation, tarsometatarsal joint
S4H3300	Open fracture-subluxation, metatarsophalangeal joint, single
S4H3400	Open fracture-subluxation, IPJ, single toe
S4H3600	Open fracture-subluxation, IPJ, multiple toes
S4J..00	Other fracture-dislocation or subluxation
S4J0.00	Other closed fracture-dislocation
S4J0000	Closed fracture-dislocation of sternum
S4J0100	Closed fracture-dislocation of pelvis
S4J1.00	Other open fracture-dislocation
S4J1000	Open fracture-dislocation of sternum
S4J1100	Open fracture-dislocation of pelvis
S4J1200	Open fracture-dislocation sterno-clavicular joint, anterior
S4J1300	Open fracture-dislocation sterno-clavicular joint, posterior
S4J2.00	Other closed fracture-subluxation
S4J2000	Closed fracture-subluxation of sternum
S4J2100	Closed fracture-subluxation of pelvis
S4J3.00	Other open fracture-subluxation
S4J3000	Open fracture-subluxation of sternum
S4J3100	Open fracture-subluxation of pelvis
S4J3200	Open fracture-subluxation sterno-clavicular joint, anterior
S4J3300	Open fracture-subluxation sterno-clavicular joint, posterior
SR1..00	Fractures involving multiple body regions
SR10.00	Fractures involving head with neck
SR10000	Closed fractures involving head with neck
SR10100	Open fractures involving head with neck
SR11.00	Fractures involving thorax with lower back and pelvis
SR12.00	Fractures involving multiple regions of one upper limb
SR12000	Closed fractures involving multiple regions of one upp limb
SR12100	Open fractures involving multiple regions of one upper limb
SR13.00	Fractures involving multiple regions of one lower limb
SR14.00	Fractures involving multiple regions of both lower limbs
SR14000	Closd fractures involving multiple regions of both low limbs
SR14100	Open fractures involving multiple regions both lower limbs
SR15000	Cl fractures involving multiple regions upper with lower lmb
SR15100	Open fracture involv multiple regions upper with lower lmb

SR16000	Closed fracture inv thorax wth low back and pelvis and limbs
SR16100	Open fracture inv thorax wth low back and pelvis and limbs
SR1z.00	Multiple fractures, unspecified
SR1z000	[X]Closed multiple fractures unspecified
SR1z100	[X]Open multiple fractures unspecified
Syu0300	[X]Fractures of other skull and facial bones
Syu0400	[X]Fracture of skull and facial bones, part unspecified
Syu1500	[X]Fracture of other specified cervical vertebra
Syu1600	[X]Fracture of other parts of neck
Syu2700	[X]Fracture of other parts of bony thorax
Syu2800	[X]Fracture of bony thorax, part unspecified
Syu4200	[X]Multiple fractures of clavicle, scapula and humerus
Syu4300	[X]Fracture of other parts of shoulder and upper arm
Syu4400	[X]Fracture of shoulder and upper arm, unspecified
Syu5300	[X]Fracture of other parts of forearm
Syu5400	[X]Fracture of forearm, unspecified
Syu6300	[X]Fracture of other carpal bone(s)
Syu6400	[X]Fracture of other metacarpal bone
Syu6500	[X]Fracture of other & unspecified parts of wrist and hand
Syu7200	[X]Fractures of other parts of femur
Syu8300	[X]Fractures of other parts of lower leg
Syu8D00	[X]Fracture of lower leg, part unspecified
Syu9400	[X]Fracture of other tarsal bones
SyuA200	[X]Fractures involving other combinations of body regions
SyuBB00	[X]Fracture of unspecified body region
TC7..00	Fracture, cause unspecified
Zw01.00	[Q] Fractures involving the epiphyseal plate
Zw02.00	[Q] Fracture type qualifying terms
Zw02400	[Q] Stress fracture
Zw02500	[Q] Refracture
Zw02D00	[Q] Open fracture grade 1
Zw02E00	[Q] Open fracture grade 2
Zw02F00	[Q] Open fracture grade 3
Zw02G00	[Q] Open fracture grade 3A
Zw02H00	[Q] Open fracture grade 3B
Zw02J00	[Q] Open fracture grade 3C

Appendix 6-1j: Read codes used to identify people with cancer

Read codes	**Cancer Read code description**
142..00	H/O: malignant neoplasm (*)
142..11	H/O: cancer
142..13	H/O: malignancy
142..15	H/O: neoplasm
1425000	H/O Malignant melanoma
B... 00	Neoplasms
B....11	Cancers
B0...00	Malignant neoplasm of lip, oral cavity and pharynx
B0...11	Carcinoma of lip, oral cavity and pharynx
B00..00	Malignant neoplasm of lip
B00..11	Carcinoma of lip
B000.00	Malignant neoplasm of upper lip, vermilion border
B000000	Malignant neoplasm of upper lip, external
B000100	Malignant neoplasm of upper lip, lipstick area
B001.00	Malignant neoplasm of lower lip, vermilion border
B001000	Malignant neoplasm of lower lip, external
B001z00	Malignant neoplasm of lower lip, vermilion border NOS

B002000	Malignant neoplasm of upper lip, buccal aspect
B002200	Malignant neoplasm of upper lip, mucosa
B002300	Malignant neoplasm of upper lip, oral aspect
B003.00	Malignant neoplasm of lower lip, inner aspect
B003000	Malignant neoplasm of lower lip, buccal aspect
B003200	Malignant neoplasm of lower lip, mucosa
B005.00	Malignant neoplasm of commissure of lip
B006.00	Malignant neoplasm of overlapping lesion of lip
B007.00	Malignant neoplasm of lip, unspecified
B00zz00	Malignant neoplasm of lip, vermilion border NOS
B01..00	Malignant neoplasm of tongue
B010.00	Malignant neoplasm of base of tongue
B010000	Malignant neoplasm of base of tongue dorsal surface
B011.00	Malignant neoplasm of dorsal surface of tongue
B011z00	Malignant neoplasm of dorsum of tongue NOS
B012.00	Malignant neoplasm of tongue, tip and lateral border
B013.00	Malignant neoplasm of ventral surface of tongue
B013100	Malignant neoplasm of frenulum linguae
B013z00	Malignant neoplasm of ventral tongue surface NOS
B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
B015.00	Malignant neoplasm of tongue, junctional zone
B016.00	Malignant neoplasm of lingual tonsil
B017.00	Malignant overlapping lesion of tongue
B01z.00	Malignant neoplasm of tongue NOS
B02..00	Malignant neoplasm of major salivary glands
B020.00	Malignant neoplasm of parotid gland
B021.00	Malignant neoplasm of submandibular gland
B022.00	Malignant neoplasm of sublingual gland
B02y.00	Malignant neoplasm of other major salivary glands
B02z.00	Malignant neoplasm of major salivary gland NOS
B03..00	Malignant neoplasm of gum
B030.00	Malignant neoplasm of upper gum
B031.00	Malignant neoplasm of lower gum
B03z.00	Malignant neoplasm of gum NOS
B04..00	Malignant neoplasm of floor of mouth
B040.00	Malignant neoplasm of anterior portion of floor of mouth
B041.00	Malignant neoplasm of lateral portion of floor of mouth
B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
B04y.00	Malignant neoplasm of other sites of floor of mouth
B04z.00	Malignant neoplasm of floor of mouth NOS
B05..00	Malignant neoplasm of other and unspecified parts of mouth
B050.00	Malignant neoplasm of cheek mucosa
B050.11	Malignant neoplasm of buccal mucosa
B051100	Malignant neoplasm of lower buccal sulcus
B052.00	Malignant neoplasm of hard palate
B053.00	Malignant neoplasm of soft palate
B054.00	Malignant neoplasm of uvula
B055.00	Malignant neoplasm of palate unspecified
B055100	Malignant neoplasm of roof of mouth
B055z00	Malignant neoplasm of palate NOS
B056.00	Malignant neoplasm of retromolar area
B057.00	Overlapping lesion of other and unspecified parts of mouth
B05y.00	Malignant neoplasm of other specified mouth parts
B05z.00	Malignant neoplasm of mouth NOS
B06..00	Malignant neoplasm of oropharynx
B060.00	Malignant neoplasm of tonsil
B060000	Malignant neoplasm of faucial tonsil
B060100	Malignant neoplasm of palatine tonsil

B060200	Malignant neoplasm of overlapping lesion of tonsil
B060z00	Malignant neoplasm tonsil NOS
B061.00	Malignant neoplasm of tonsillar fossa
B062.00	Malignant neoplasm of tonsillar pillar
B062000	Malignant neoplasm of faucial pillar
B062200	Malignant neoplasm of palatoglossal arch
B062z00	Malignant neoplasm of tonsillar fossa NOS
B063.00	Malignant neoplasm of vallecula
B064.00	Malignant neoplasm of anterior epiglottis
B064000	Malignant neoplasm of epiglottis, free border
B064100	Malignant neoplasm of glossoepiglottic fold
B064z00	Malignant neoplasm of anterior epiglottis NOS
B065.00	Malignant neoplasm of junctional region of epiglottis
B066.00	Malignant neoplasm of lateral wall of oropharynx
B06y.00	Malignant neoplasm of oropharynx, other specified sites
B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
B06z.00	Malignant neoplasm of oropharynx NOS
B07..00	Malignant neoplasm of nasopharynx
B070.00	Malignant neoplasm of roof of nasopharynx
B071.00	Malignant neoplasm of posterior wall of nasopharynx
B071000	Malignant neoplasm of adenoid
B071100	Malignant neoplasm of pharyngeal tonsil
B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
B072000	Malignant neoplasm of pharyngeal recess
B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
B073.00	Malignant neoplasm of anterior wall of nasopharynx
B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
B07z.00	Malignant neoplasm of nasopharynx NOS
B08..00	Malignant neoplasm of hypopharynx
B080.00	Malignant neoplasm of postcricoid region
B081.00	Malignant neoplasm of pyriform sinus
B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
B083.00	Malignant neoplasm of posterior pharynx
B08y.00	Malignant neoplasm of other specified hypopharyngeal site
B08z.00	Malignant neoplasm of hypopharynx NOS
B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
B0z0.00	Malignant neoplasm of pharynx unspecified
B0z2.00	Malignant neoplasm of laryngopharynx
B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
B1...00	Malignant neoplasm of digestive organs and peritoneum
B1...11	Carcinoma of digestive organs and peritoneum
B10..00	Malignant neoplasm of oesophagus
B100.00	Malignant neoplasm of cervical oesophagus
B101.00	Malignant neoplasm of thoracic oesophagus
B102.00	Malignant neoplasm of abdominal oesophagus
B103.00	Malignant neoplasm of upper third of oesophagus
B104.00	Malignant neoplasm of middle third of oesophagus
B105.00	Malignant neoplasm of lower third of oesophagus
B106.00	Malignant neoplasm, overlapping lesion of oesophagus
B10y.00	Malignant neoplasm of other specified part of oesophagus
B10z.00	Malignant neoplasm of oesophagus NOS
B10z.11	Oesophageal cancer
B11..00	Malignant neoplasm of stomach
B11..11	Gastric neoplasm
B110.00	Malignant neoplasm of cardia of stomach
B110000	Malignant neoplasm of cardiac orifice of stomach
B110100	Malignant neoplasm of cardio-oesophageal junction of stomach

B110z00	Malignant neoplasm of cardia of stomach NOS
B111.00	Malignant neoplasm of pylorus of stomach
B111000	Malignant neoplasm of prepylorus of stomach
B111100	Malignant neoplasm of pyloric canal of stomach
B111z00	Malignant neoplasm of pylorus of stomach NOS
B112.00	Malignant neoplasm of pyloric antrum of stomach
B113.00	Malignant neoplasm of fundus of stomach
B114.00	Malignant neoplasm of body of stomach
B115.00	Malignant neoplasm of lesser curve of stomach unspecified
B116.00	Malignant neoplasm of greater curve of stomach unspecified
B117.00	Malignant neoplasm, overlapping lesion of stomach
B11y.00	Malignant neoplasm of other specified site of stomach
B11yz00	Malignant neoplasm of other specified site of stomach NOS
B11z.00	Malignant neoplasm of stomach NOS
B12..00	Malignant neoplasm of small intestine and duodenum
B120.00	Malignant neoplasm of duodenum
B121.00	Malignant neoplasm of jejunum
B122.00	Malignant neoplasm of ileum
B123.00	Malignant neoplasm of Meckel's diverticulum
B124.00	Malignant neoplasm, overlapping lesion of small intestine
B12y.00	Malignant neoplasm of other specified site small intestine
B12z.00	Malignant neoplasm of small intestine NOS
B13..00	Malignant neoplasm of colon
B130.00	Malignant neoplasm of hepatic flexure of colon
B131.00	Malignant neoplasm of transverse colon
B132.00	Malignant neoplasm of descending colon
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B134.11	Carcinoma of caecum
B135.00	Malignant neoplasm of appendix
B136.00	Malignant neoplasm of ascending colon
B137.00	Malignant neoplasm of splenic flexure of colon
B138.00	Malignant neoplasm, overlapping lesion of colon
B13y.00	Malignant neoplasm of other specified sites of colon
B13z.00	Malignant neoplasm of colon NOS
B13z.11	Colonic cancer
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B140.00	Malignant neoplasm of rectosigmoid junction
B141.00	Malignant neoplasm of rectum
B141.11	Carcinoma of rectum
B141.12	Rectal carcinoma
B142.00	Malignant neoplasm of anal canal
B142.11	Anal carcinoma
B142000	Malignant neoplasm of cloacogenic zone
B143.00	Malignant neoplasm of anus unspecified
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
B150.00	Primary malignant neoplasm of liver
B150000	Primary carcinoma of liver
B150100	Hepatoblastoma of liver
B150200	Primary angiosarcoma of liver
B150300	Hepatocellular carcinoma
B150z00	Primary malignant neoplasm of liver NOS
B151.00	Malignant neoplasm of intrahepatic bile ducts
B151000	Malignant neoplasm of interlobular bile ducts
B151200	Malignant neoplasm of intrahepatic biliary passages
B151400	Malignant neoplasm of intrahepatic gall duct

B152.00	Malignant neoplasm of liver unspecified
B153.00	Secondary malignant neoplasm of liver
B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
B160.00	Malignant neoplasm of gallbladder
B160.11	Carcinoma gallbladder
B161.00	Malignant neoplasm of extrahepatic bile ducts
B161100	Malignant neoplasm of hepatic duct
B161200	Malignant neoplasm of common bile duct
B161211	Carcinoma common bile duct
B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
B162.00	Malignant neoplasm of ampulla of Vater
B163.00	Malignant neoplasm, overlapping lesion of biliary tract
B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
B17..00	Malignant neoplasm of pancreas
B170.00	Malignant neoplasm of head of pancreas
B171.00	Malignant neoplasm of body of pancreas
B172.00	Malignant neoplasm of tail of pancreas
B173.00	Malignant neoplasm of pancreatic duct
B174.00	Malignant neoplasm of Islets of Langerhans
B175.00	Malignant neoplasm, overlapping lesion of pancreas
B17y.00	Malignant neoplasm of other specified sites of pancreas
B17y000	Malignant neoplasm of ectopic pancreatic tissue
B17z.00	Malignant neoplasm of pancreas NOS
B18..00	Malignant neoplasm of retroperitoneum and peritoneum
B180.00	Malignant neoplasm of retroperitoneum
B180100	Malignant neoplasm of perinephric tissue
B180200	Malignant neoplasm of retrocaecal tissue
B180z00	Malignant neoplasm of retroperitoneum NOS
B181.00	Mesothelioma of peritoneum
B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
B18y.00	Malignant neoplasm of specified parts of peritoneum
B18y300	Malignant neoplasm of omentum
B18y400	Malignant neoplasm of parietal peritoneum
B18y500	Malignant neoplasm of pelvic peritoneum
B18y600	Malignant neoplasm of the pouch of Douglas
B18y700	Malignant neoplasm of mesentery
B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
B1z0.11	Cancer of bowel
B1z1.00	Malignant neoplasm of spleen NEC
B1z1z00	Malignant neoplasm of spleen NOS
B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
B2...00	Malig neop of respiratory tract and intrathoracic organs
B2...11	Carcinoma of respiratory tract and intrathoracic organs
B20..00	Malig neop nasal cavities, middle ear and accessory sinuses
B200.00	Malignant neoplasm of nasal cavities
B200200	Malignant neoplasm of septum of nose
B200300	Malignant neoplasm of vestibule of nose
B200z00	Malignant neoplasm of nasal cavities NOS
B201.00	Malig neop auditory tube, middle ear and mastoid air cells
B201100	Malignant neoplasm of tympanic cavity
B201300	Malignant neoplasm of mastoid air cells

B202.00	Malignant neoplasm of maxillary sinus
B203.00	Malignant neoplasm of ethmoid sinus
B204.00	Malignant neoplasm of frontal sinus
B205.00	Malignant neoplasm of sphenoidal sinus
B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
B20z.00	Malignant neoplasm of accessory sinus NOS
B21..00	Malignant neoplasm of larynx
B210.00	Malignant neoplasm of glottis
B211.00	Malignant neoplasm of supraglottis
B212.00	Malignant neoplasm of subglottis
B213.00	Malignant neoplasm of laryngeal cartilage
B213000	Malignant neoplasm of arytenoid cartilage
B213100	Malignant neoplasm of cricoid cartilage
B213300	Malignant neoplasm of thyroid cartilage
B214.00	Malignant neoplasm, overlapping lesion of larynx
B215.00	Malignant neoplasm of epiglottis NOS
B21y.00	Malignant neoplasm of larynx, other specified site
B21z.00	Malignant neoplasm of larynx NOS
B22..00	Malignant neoplasm of trachea, bronchus and lung
B220.00	Malignant neoplasm of trachea
B220z00	Malignant neoplasm of trachea NOS
B221.00	Malignant neoplasm of main bronchus
B221000	Malignant neoplasm of carina of bronchus
B221100	Malignant neoplasm of hilus of lung
B221z00	Malignant neoplasm of main bronchus NOS
B222.00	Malignant neoplasm of upper lobe, bronchus or lung
B222.11	Pancoast's syndrome
B222000	Malignant neoplasm of upper lobe bronchus
B222100	Malignant neoplasm of upper lobe of lung
B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
B223.00	Malignant neoplasm of middle lobe, bronchus or lung
B223000	Malignant neoplasm of middle lobe bronchus
B223100	Malignant neoplasm of middle lobe of lung
B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
B224.00	Malignant neoplasm of lower lobe, bronchus or lung
B224000	Malignant neoplasm of lower lobe bronchus
B224100	Malignant neoplasm of lower lobe of lung
B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
B226.00	Mesothelioma
B22y.00	Malignant neoplasm of other sites of bronchus or lung
B22z.00	Malignant neoplasm of bronchus or lung NOS
B22z.11	Lung cancer
B23..00	Malignant neoplasm of pleura
B230.00	Malignant neoplasm of parietal pleura
B231.00	Malignant neoplasm of visceral pleura
B232.00	Mesothelioma of pleura
B23z.00	Malignant neoplasm of pleura NOS
B24..00	Malignant neoplasm of thymus, heart and mediastinum
B240.00	Malignant neoplasm of thymus
B241000	Malignant neoplasm of endocardium
B241200	Malignant neoplasm of myocardium
B241400	Mesothelioma of pericardium
B242.00	Malignant neoplasm of anterior mediastinum
B243.00	Malignant neoplasm of posterior mediastinum
B24X.00	Malignant neoplasm of mediastinum, part unspecified
B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS

B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
B2z0.00	Malig neop of upper respiratory tract, part unspecified
B2zz.00	Malignant neoplasm of respiratory tract NOS
B3...00	Malig neop of bone, connective tissue, skin and breast
B3...11	Carcinoma of bone, connective tissue, skin and breast
B3...12	Sarcoma of bone and connective tissue
B30..00	Malignant neoplasm of bone and articular cartilage
B30..11	Chondroma
B30..12	Osteoma
B300.00	Malignant neoplasm of bones of skull and face
B300200	Malignant neoplasm of malar bone
B300400	Malignant neoplasm of occipital bone
B300500	Malignant neoplasm of orbital bone
B300600	Malignant neoplasm of parietal bone
B300700	Malignant neoplasm of sphenoid bone
B300800	Malignant neoplasm of temporal bone
B300900	Malignant neoplasm of zygomatic bone
B300A00	Malignant neoplasm of maxilla
B300C00	Malignant neoplasm of vomer
B300z00	Malignant neoplasm of bones of skull and face NOS
B301.00	Malignant neoplasm of mandible
B302.00	Malignant neoplasm of vertebral column
B302000	Malignant neoplasm of cervical vertebra
B302100	Malignant neoplasm of thoracic vertebra
B302200	Malignant neoplasm of lumbar vertebra
B302z00	Malignant neoplasm of vertebral column NOS
B303.00	Malignant neoplasm of ribs, sternum and clavicle
B303000	Malignant neoplasm of rib
B303100	Malignant neoplasm of sternum
B303200	Malignant neoplasm of clavicle
B303300	Malignant neoplasm of costal cartilage
B303400	Malignant neoplasm of costo-vertebral joint
B303500	Malignant neoplasm of xiphoid process
B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
B304.00	Malignant neoplasm of scapula and long bones of upper arm
B304000	Malignant neoplasm of scapula
B304200	Malignant neoplasm of humerus
B305.12	Malignant neoplasm of metacarpal bones
B305000	Malignant neoplasm of carpal bone - scaphoid
B305100	Malignant neoplasm of carpal bone - lunate
B305D00	Malignant neoplasm of phalanges of hand
B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
B306000	Malignant neoplasm of ilium
B306100	Malignant neoplasm of ischium
B306300	Malignant neoplasm of sacral vertebra
B306400	Malignant neoplasm of coccygeal vertebra
B306500	Malignant sacral teratoma
B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
B307.00	Malignant neoplasm of long bones of leg
B307000	Malignant neoplasm of femur
B307100	Malignant neoplasm of fibula
B307200	Malignant neoplasm of tibia
B307z00	Malignant neoplasm of long bones of leg NOS
B308D00	Malignant neoplasm of phalanges of foot
B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd

B30z.00	Malignant neoplasm of bone and articular cartilage NOS
B30z000	Osteosarcoma
B31..00	Malignant neoplasm of connective and other soft tissue
B310.00	Malig neop of connective and soft tissue head, face and neck
B310000	Malignant neoplasm of soft tissue of head
B310100	Malignant neoplasm of soft tissue of face
B310200	Malignant neoplasm of soft tissue of neck
B310300	Malignant neoplasm of cartilage of ear
B310400	Malignant neoplasm of tarsus of eyelid
B310z00	Malig neop connective and soft tissue head, face, neck NOS
B311.00	Malig neop connective and soft tissue upper limb/shoulder
B311000	Malignant neoplasm of connective and soft tissue of shoulder
B311100	Malignant neoplasm of connective and soft tissue, upper arm
B311200	Malignant neoplasm of connective and soft tissue of fore-arm
B311300	Malignant neoplasm of connective and soft tissue of hand
B311400	Malignant neoplasm of connective and soft tissue of finger
B311500	Malignant neoplasm of connective and soft tissue of thumb
B312.00	Malig neop of connective and soft tissue of hip and leg
B312100	Malig neop of connective and soft tissue thigh and upper leg
B312200	Malig neop connective and soft tissue of popliteal space
B312300	Malig neop of connective and soft tissue of lower leg
B312400	Malignant neoplasm of connective and soft tissue of foot
B312z00	Malig neop connective and soft tissue hip and leg NOS
B313.00	Malignant neoplasm of connective and soft tissue of thorax
B313000	Malignant neoplasm of connective and soft tissue of axilla
B313200	Malignant neoplasm of great vessels
B313z00	Malig neop of connective and soft tissue of thorax NOS
B314.00	Malignant neoplasm of connective and soft tissue of abdomen
B314000	Malig neop of connective and soft tissue of abdominal wall
B314z00	Malig neop of connective and soft tissue of abdomen NOS
B315.00	Malignant neoplasm of connective and soft tissue of pelvis
B315000	Malignant neoplasm of connective and soft tissue of buttock
B315100	Malig neop of connective and soft tissue of inguinal region
B315200	Malignant neoplasm of connective and soft tissue of perineum
B315z00	Malig neop of connective and soft tissue of pelvis NOS
B316.00	Malig neop of connective and soft tissue trunk unspecified
B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
B32..00	Malignant melanoma of skin
B320.00	Malignant melanoma of lip
B321.00	Malignant melanoma of eyelid including canthus
B322.00	Malignant melanoma of ear and external auricular canal
B322000	Malignant melanoma of auricle (ear)
B323.00	Malignant melanoma of other and unspecified parts of face
B323000	Malignant melanoma of external surface of cheek
B323100	Malignant melanoma of chin
B323200	Malignant melanoma of eyebrow
B323300	Malignant melanoma of forehead
B323400	Malignant melanoma of external surface of nose
B323500	Malignant melanoma of temple
B323z00	Malignant melanoma of face NOS
B324.00	Malignant melanoma of scalp and neck
B324000	Malignant melanoma of scalp
B324100	Malignant melanoma of neck
B325.00	Malignant melanoma of trunk (excluding scrotum)
B325000	Malignant melanoma of axilla
B325100	Malignant melanoma of breast
B325200	Malignant melanoma of buttock
B325300	Malignant melanoma of groin

B325400	Malignant melanoma of perianal skin
B325500	Malignant melanoma of perineum
B325600	Malignant melanoma of umbilicus
B325700	Malignant melanoma of back
B325800	Malignant melanoma of chest wall
B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
B326.00	Malignant melanoma of upper limb and shoulder
B326000	Malignant melanoma of shoulder
B326100	Malignant melanoma of upper arm
B326200	Malignant melanoma of fore-arm
B326300	Malignant melanoma of hand
B326400	Malignant melanoma of finger
B326500	Malignant melanoma of thumb
B326z00	Malignant melanoma of upper limb or shoulder NOS
B327.00	Malignant melanoma of lower limb and hip
B327100	Malignant melanoma of thigh
B327200	Malignant melanoma of knee
B327300	Malignant melanoma of popliteal fossa area
B327400	Malignant melanoma of lower leg
B327500	Malignant melanoma of ankle
B327600	Malignant melanoma of heel
B327700	Malignant melanoma of foot
B327800	Malignant melanoma of toe
B327900	Malignant melanoma of great toe
B327z00	Malignant melanoma of lower limb or hip NOS
B32y.00	Malignant melanoma of other specified skin site
B32z.00	Malignant melanoma of skin NOS
B33..00	Other malignant neoplasm of skin
B33..11	Basal cell carcinoma
B33..12	Epithelioma
B33..13	Rodent ulcer
B33..14	Malignant neoplasm of sebaceous gland
B33..15	Malignant neoplasm of sweat gland
B33..16	Epithelioma basal cell
B330.00	Malignant neoplasm of skin of lip
B331.00	Malignant neoplasm of eyelid including canthus
B331000	Malignant neoplasm of canthus
B331100	Malignant neoplasm of upper eyelid
B331200	Malignant neoplasm of lower eyelid
B332.00	Malignant neoplasm skin of ear and external auricular canal
B332000	Malignant neoplasm of skin of auricle (ear)
B332100	Malignant neoplasm of skin of external auditory meatus
B332200	Malignant neoplasm of pinna NEC
B332z00	Malig neop skin of ear and external auricular canal NOS
B333.00	Malignant neoplasm skin of other and unspecified parts face
B333000	Malignant neoplasm of skin of cheek, external
B333100	Malignant neoplasm of skin of chin
B333200	Malignant neoplasm of skin of eyebrow
B333300	Malignant neoplasm of skin of forehead
B333400	Malignant neoplasm of skin of nose (external)
B333500	Malignant neoplasm of skin of temple
B333z00	Malignant neoplasm skin other and unspec part of face NOS
B334.00	Malignant neoplasm of scalp and skin of neck
B334000	Malignant neoplasm of scalp
B334100	Malignant neoplasm of skin of neck
B334z00	Malignant neoplasm of scalp or skin of neck NOS
B335.00	Malignant neoplasm of skin of trunk, excluding scrotum
B335000	Malignant neoplasm of skin of axillary fold

B335100	Malignant neoplasm of skin of chest, excluding breast
B335200	Malignant neoplasm of skin of breast
B335300	Malignant neoplasm of skin of abdominal wall
B335500	Malignant neoplasm of skin of groin
B335600	Malignant neoplasm of skin of perineum
B335700	Malignant neoplasm of skin of back
B335800	Malignant neoplasm of skin of buttock
B335900	Malignant neoplasm of perianal skin
B335A00	Malignant neoplasm of skin of scapular region
B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
B336.00	Malignant neoplasm of skin of upper limb and shoulder
B336000	Malignant neoplasm of skin of shoulder
B336100	Malignant neoplasm of skin of upper arm
B336200	Malignant neoplasm of skin of fore-arm
B336300	Malignant neoplasm of skin of hand
B336400	Malignant neoplasm of skin of finger
B336500	Malignant neoplasm of skin of thumb
B336z00	Malignant neoplasm of skin of upper limb or shoulder NOS
B337.00	Malignant neoplasm of skin of lower limb and hip
B337000	Malignant neoplasm of skin of hip
B337100	Malignant neoplasm of skin of thigh
B337200	Malignant neoplasm of skin of knee
B337300	Malignant neoplasm of skin of popliteal fossa area
B337400	Malignant neoplasm of skin of lower leg
B337500	Malignant neoplasm of skin of ankle
B337700	Malignant neoplasm of skin of foot
B337800	Malignant neoplasm of skin of toe
B337900	Malignant neoplasm of skin of great toe
B337z00	Malignant neoplasm of skin of lower limb or hip NOS
B338.00	Squamous cell carcinoma of skin
B339.00	Dermatofibrosarcoma protuberans
B33X.00	Malignant neoplasm overlapping lesion of skin
B33y.00	Malignant neoplasm of other specified skin sites
B33z.00	Malignant neoplasm of skin NOS
B33z.11	Squamous cell carcinoma of skin NOS
B33z000	Kaposi's sarcoma of skin
B33z100	Naevoid basal cell carcinoma syndrome
B33z111	Basal cell naevus syndrome
B34..00	Malignant neoplasm of female breast
B34..11	Ca female breast
B340.00	Malignant neoplasm of nipple and areola of female breast
B340000	Malignant neoplasm of nipple of female breast
B340100	Malignant neoplasm of areola of female breast
B340z00	Malignant neoplasm of nipple or areola of female breast NOS
B341.00	Malignant neoplasm of central part of female breast
B342.00	Malignant neoplasm of upper-inner quadrant of female breast
B343.00	Malignant neoplasm of lower-inner quadrant of female breast
B344.00	Malignant neoplasm of upper-outer quadrant of female breast
B345.00	Malignant neoplasm of lower-outer quadrant of female breast
B346.00	Malignant neoplasm of axillary tail of female breast
B347.00	Malignant neoplasm, overlapping lesion of breast
B34y.00	Malignant neoplasm of other site of female breast
B34yz00	Malignant neoplasm of other site of female breast NOS
B34z.00	Malignant neoplasm of female breast NOS
B35..00	Malignant neoplasm of male breast
B350.00	Malignant neoplasm of nipple and areola of male breast
B350000	Malignant neoplasm of nipple of male breast
B350100	Malignant neoplasm of areola of male breast

B35zz00	Malignant neoplasm of male breast NOS
B3y..00	Malig neop of bone, connective tissue, skin and breast OS
B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
B4...00	Malignant neoplasm of genitourinary organ
B4...11	Carcinoma of genitourinary organ
B40..00	Malignant neoplasm of uterus, part unspecified
B41..00	Malignant neoplasm of cervix uteri
B41..11	Cervical carcinoma (uterus)
B410.00	Malignant neoplasm of endocervix
B410000	Malignant neoplasm of endocervical canal
B410100	Malignant neoplasm of endocervical gland
B410z00	Malignant neoplasm of endocervix NOS
B411.00	Malignant neoplasm of exocervix
B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
B41y.00	Malignant neoplasm of other site of cervix
B41y000	Malignant neoplasm of cervical stump
B41y100	Malignant neoplasm of squamocolumnar junction of cervix
B41yz00	Malignant neoplasm of other site of cervix NOS
B41z.00	Malignant neoplasm of cervix uteri NOS
B42..00	Malignant neoplasm of placenta
B420.00	Choriocarcinoma
B43..00	Malignant neoplasm of body of uterus
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
B430000	Malignant neoplasm of cornu of corpus uteri
B430100	Malignant neoplasm of fundus of corpus uteri
B430200	Malignant neoplasm of endometrium of corpus uteri
B430211	Malignant neoplasm of endometrium
B430300	Malignant neoplasm of myometrium of corpus uteri
B430z00	Malignant neoplasm of corpus uteri NOS
B431.00	Malignant neoplasm of isthmus of uterine body
B431000	Malignant neoplasm of lower uterine segment
B431z00	Malignant neoplasm of isthmus of uterine body NOS
B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
B43y.00	Malignant neoplasm of other site of uterine body
B43z.00	Malignant neoplasm of body of uterus NOS
B44..00	Malignant neoplasm of ovary and other uterine adnexa
B440.00	Malignant neoplasm of ovary
B440.11	Cancer of ovary
B441.00	Malignant neoplasm of fallopian tube
B443.00	Malignant neoplasm of parametrium
B444.00	Malignant neoplasm of round ligament
B44y.00	Malignant neoplasm of other site of uterine adnexa
B44z.00	Malignant neoplasm of uterine adnexa NOS
B45..00	Malig neop of other and unspecified female genital organs
B450.00	Malignant neoplasm of vagina
B450100	Malignant neoplasm of vaginal vault
B450z00	Malignant neoplasm of vagina NOS
B451.00	Malignant neoplasm of labia majora
B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
B451z00	Malignant neoplasm of labia majora NOS
B452.00	Malignant neoplasm of labia minora
B453.00	Malignant neoplasm of clitoris
B454.00	Malignant neoplasm of vulva unspecified
B454.11	Primary vulval cancer
B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
B45y000	Malignant neoplasm of overlapping lesion of vulva
B45z.00	Malignant neoplasm of female genital organ NOS
B46..00	Malignant neoplasm of prostate

B47..00	Malignant neoplasm of testis
B470.00	Malignant neoplasm of undescended testis
B470200	Seminoma of undescended testis
B470300	Teratoma of undescended testis
B471.00	Malignant neoplasm of descended testis
B471000	Seminoma of descended testis
B471100	Teratoma of descended testis
B471z00	Malignant neoplasm of descended testis NOS
B47z.00	Malignant neoplasm of testis NOS
B47z.11	Seminoma of testis
B47z.12	Teratoma of testis
B48..00	Malignant neoplasm of penis and other male genital organs
B480.00	Malignant neoplasm of prepuce (foreskin)
B481.00	Malignant neoplasm of glans penis
B482.00	Malignant neoplasm of body of penis
B483.00	Malignant neoplasm of penis, part unspecified
B484.00	Malignant neoplasm of epididymis
B485.00	Malignant neoplasm of spermatic cord
B486.00	Malignant neoplasm of scrotum
B487.00	Malignant neoplasm, overlapping lesion of penis
B48y.00	Malignant neoplasm of other male genital organ
B48y000	Malignant neoplasm of seminal vesicle
B48y100	Malignant neoplasm of tunica vaginalis
B48y200	Malignant neoplasm, overlapping lesion male genital orgs
B48yz00	Malignant neoplasm of other male genital organ NOS
B48z.00	Malignant neoplasm of penis and other male genital organ NOS
B49..00	Malignant neoplasm of urinary bladder
B490.00	Malignant neoplasm of trigone of urinary bladder
B491.00	Malignant neoplasm of dome of urinary bladder
B492.00	Malignant neoplasm of lateral wall of urinary bladder
B493.00	Malignant neoplasm of anterior wall of urinary bladder
B494.00	Malignant neoplasm of posterior wall of urinary bladder
B495.00	Malignant neoplasm of bladder neck
B496.00	Malignant neoplasm of ureteric orifice
B497.00	Malignant neoplasm of urachus
B49y.00	Malignant neoplasm of other site of urinary bladder
B49y000	Malignant neoplasm, overlapping lesion of bladder
B49z.00	Malignant neoplasm of urinary bladder NOS
B4A..00	Malig neop of kidney and other unspecified urinary organs
B4A..11	Renal malignant neoplasm
B4A0.00	Malignant neoplasm of kidney parenchyma
B4A0000	Hypernephroma
B4A1.00	Malignant neoplasm of renal pelvis
B4A1000	Malignant neoplasm of renal calyces
B4A1z00	Malignant neoplasm of renal pelvis NOS
B4A2.00	Malignant neoplasm of ureter
B4A3.00	Malignant neoplasm of urethra
B4Ay.00	Malignant neoplasm of other urinary organs
B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
B4y..00	Malignant neoplasm of genitourinary organ OS
B4z..00	Malignant neoplasm of genitourinary organ NOS
B5...00	Malignant neoplasm of other and unspecified sites
B5...11	Carcinoma of other and unspecified sites
B50..00	Malignant neoplasm of eye
B500000	Malignant neoplasm of ciliary body
B500100	Malignant neoplasm of iris
B500z00	Malignant neoplasm of eyeball NOS
B501.00	Malignant neoplasm of orbit

B501z00	Malignant neoplasm of orbit NOS
B502.00	Malignant neoplasm of lacrimal gland
B503.00	Malignant neoplasm of conjunctiva
B504.00	Malignant neoplasm of cornea
B505.00	Malignant neoplasm of retina
B506.00	Malignant neoplasm of choroid
B507.00	Malignant neoplasm of lacrimal duct
B507100	Malignant neoplasm of nasolacrimal duct
B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
B50y.00	Malignant neoplasm of other specified site of eye
B50z.00	Malignant neoplasm of eye NOS
B51..00	Malignant neoplasm of brain
B51..11	Cerebral tumour - malignant
B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
B510000	Malignant neoplasm of basal ganglia
B510100	Malignant neoplasm of cerebral cortex
B510400	Malignant neoplasm of hypothalamus
B510500	Malignant neoplasm of thalamus
B510z00	Malignant neoplasm of cerebrum NOS
B511.00	Malignant neoplasm of frontal lobe
B512.00	Malignant neoplasm of temporal lobe
B512000	Malignant neoplasm of hippocampus
B512z00	Malignant neoplasm of temporal lobe NOS
B513.00	Malignant neoplasm of parietal lobe
B514.00	Malignant neoplasm of occipital lobe
B515.00	Malignant neoplasm of cerebral ventricles
B515000	Malignant neoplasm of choroid plexus
B516.00	Malignant neoplasm of cerebellum
B517.00	Malignant neoplasm of brain stem
B517000	Malignant neoplasm of cerebral peduncle
B517100	Malignant neoplasm of medulla oblongata
B517300	Malignant neoplasm of pons
B517z00	Malignant neoplasm of brain stem NOS
B51y.00	Malignant neoplasm of other parts of brain
B51y000	Malignant neoplasm of corpus callosum
B51z.00	Malignant neoplasm of brain NOS
B52..00	Malig neop of other and unspecified parts of nervous system
B520.00	Malignant neoplasm of cranial nerves
B520100	Malignant neoplasm of optic nerve
B520200	Malignant neoplasm of acoustic nerve
B520z00	Malignant neoplasm of cranial nerves NOS
B521.00	Malignant neoplasm of cerebral meninges
B522.00	Malignant neoplasm of spinal cord
B523.00	Malignant neoplasm of spinal meninges
B523z00	Malignant neoplasm of spinal meninges NOS
B524.00	Malig neopl peripheral nerves and autonomic nervous system
B524000	Malignant neoplasm of peripheral nerves of head, face & neck
B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
B524500	Malignant neoplasm of peripheral nerve of pelvis
B525.00	Malignant neoplasm of cauda equina
B52W.00	Malig neopl, overlap lesion brain & other part of CNS
B52X.00	Malignant neoplasm of meninges, unspecified
B52y.00	Malignant neoplasm of other specified part of nervous system
B52z.00	Malignant neoplasm of nervous system NOS
B53..00	Malignant neoplasm of thyroid gland
B54..00	Malig neop of other endocrine glands and related structures
B540.00	Malignant neoplasm of adrenal gland

B540.11	Phaeochromocytoma
B540000	Malignant neoplasm of adrenal cortex
B540z00	Malignant neoplasm of adrenal gland NOS
B541.00	Malignant neoplasm of parathyroid gland
B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
B542000	Malignant neoplasm of pituitary gland
B542100	Malignant neoplasm of craniopharyngeal duct
B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
B543.00	Malignant neoplasm of pineal gland
B544.00	Malignant neoplasm of carotid body
B545.00	Malignant neoplasm of aortic body and other paraganglia
B545000	Malignant neoplasm of glomus jugulare
B545100	Malignant neoplasm of aortic body
B545200	Malignant neoplasm of coccygeal body
B54y.00	Malignant neoplasm of other specified endocrine gland
B54z.00	Malig neop of endocrine gland or related structure NOS
B55..00	Malignant neoplasm of other and ill-defined sites
B550.00	Malignant neoplasm of head, neck and face
B550000	Malignant neoplasm of head NOS
B550100	Malignant neoplasm of cheek NOS
B550200	Malignant neoplasm of nose NOS
B550300	Malignant neoplasm of jaw NOS
B550400	Malignant neoplasm of neck NOS
B550500	Malignant neoplasm of supraclavicular fossa NOS
B550z00	Malignant neoplasm of head, neck and face NOS
B551.00	Malignant neoplasm of thorax
B551000	Malignant neoplasm of axilla NOS
B551100	Malignant neoplasm of chest wall NOS
B551z00	Malignant neoplasm of thorax NOS
B552.00	Malignant neoplasm of abdomen
B553.00	Malignant neoplasm of pelvis
B553000	Malignant neoplasm of inguinal region NOS
B553100	Malignant neoplasm of presacral region
B553z00	Malignant neoplasm of pelvis NOS
B554.00	Malignant neoplasm of upper limb NOS
B555.00	Malignant neoplasm of lower limb NOS
B55y.00	Malignant neoplasm of other specified sites
B55y000	Malignant neoplasm of back NOS
B55y100	Malignant neoplasm of trunk NOS
B55yz00	Malignant neoplasm of specified site NOS
B55z.00	Malignant neoplasm of other and ill defined site NOS
B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
B56..11	Lymph node metastases
B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
B560000	Secondary and unspec malig neop of superficial parotid LN
B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
B560200	Secondary and unspec malig neop superficial cervical LN
B560300	Secondary and unspec malignant neoplasm occipital lymph node
B560400	Secondary and unspec malig neop deep parotid lymph nodes
B560500	Secondary and unspec malig neop submandibular lymph nodes
B560700	Secondary and unspec malig neop submental lymph nodes
B560800	Secondary and unspec malig neop anterior cervical LN
B560900	Secondary and unspec malig neop deep cervical LN
B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
B561000	Secondary and unspec malig neop internal mammary lymph nodes
B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
B561400	Secondary and unspec malig neop post mediastinal lymph nodes

B561500	Secondary and unspec malig neop paratracheal lymph nodes
B561600	Secondary and unspec malig neop superfic tracheobronchial LN
B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
B561900	Secondary and unspec malig neop pulmonary lymph nodes
B561z00	Secondary and unspec malig neop intrathoracic LN NOS
B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
B562100	Secondary and unspec malig neop superficial mesenteric LN
B562200	Secondary and unspec malig neop inferior mesenteric LN
B562300	Secondary and unspec malig neop common iliac lymph nodes
B562400	Secondary and unspec malig neop external iliac lymph nodes
B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
B563.00	Secondary and unspec malig neop axilla and upper limb LN
B563000	Secondary and unspec malig neop axillary lymph nodes
B563200	Secondary and unspec malig neop infraclavicular lymph nodes
B563300	Secondary and unspec malig neop pectoral lymph nodes
B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
B564.00	Secondary and unspec malig neop inguinal and lower limb LN
B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
B565200	Secondary and unspec malig neop circumflex iliac LN
B565z00	Secondary and unspec malig neop intrapelvic LN NOS
B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
B56z.00	Secondary and unspec malig neop lymph nodes NOS
B57..00	Secondary malig neop of respiratory and digestive systems
B57..11	Metastases of respiratory and/or digestive systems
B57..12	Secondary carcinoma of respiratory and/or digestive systems
B570.00	Secondary malignant neoplasm of lung
B571.00	Secondary malignant neoplasm of mediastinum
B572.00	Secondary malignant neoplasm of pleura
B573.00	Secondary malignant neoplasm of other respiratory organs
B574.00	Secondary malignant neoplasm of small intestine and duodenum
B574000	Secondary malignant neoplasm of duodenum
B574z00	Secondary malig neop of small intestine or duodenum NOS
B575.00	Secondary malignant neoplasm of large intestine and rectum
B575000	Secondary malignant neoplasm of colon
B575z00	Secondary malig neop of large intestine or rectum NOS
B576.00	Secondary malig neop of retroperitoneum and peritoneum
B576000	Secondary malignant neoplasm of retroperitoneum
B576100	Secondary malignant neoplasm of peritoneum
B576200	Malignant ascites
B577.00	Secondary malignant neoplasm of liver
B577.11	Liver metastases
B57y.00	Secondary malignant neoplasm of other digestive organ
B57z.00	Secondary malig neop of respiratory or digestive system NOS
B58..00	Secondary malignant neoplasm of other specified sites
B58..11	Secondary carcinoma of other specified sites
B580.00	Secondary malignant neoplasm of kidney
B581.00	Secondary malignant neoplasm of other urinary organs
B581000	Secondary malignant neoplasm of ureter
B581100	Secondary malignant neoplasm of bladder
B581200	Secondary malignant neoplasm of urethra
B581z00	Secondary malignant neoplasm of other urinary organ NOS
B582.00	Secondary malignant neoplasm of skin
B582000	Secondary malignant neoplasm of skin of head
B582100	Secondary malignant neoplasm of skin of face
B582200	Secondary malignant neoplasm of skin of neck
B582300	Secondary malignant neoplasm of skin of trunk
B582400	Secondary malignant neoplasm of skin of shoulder and arm

B582500	Secondary malignant neoplasm of skin of hip and leg
B582600	Secondary malignant neoplasm of skin of breast
B582z00	Secondary malignant neoplasm of skin NOS
B583.00	Secondary malignant neoplasm of brain and spinal cord
B583000	Secondary malignant neoplasm of brain
B583100	Secondary malignant neoplasm of spinal cord
B583200	Cerebral metastasis
B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
B584.00	Secondary malignant neoplasm of other part of nervous system
B585.00	Secondary malignant neoplasm of bone and bone marrow
B585000	Pathological fracture due to metastatic bone disease
B586.00	Secondary malignant neoplasm of ovary
B587.00	Secondary malignant neoplasm of adrenal gland
B58y.00	Secondary malignant neoplasm of other specified sites
B58y000	Secondary malignant neoplasm of breast
B58y100	Secondary malignant neoplasm of uterus
B58y200	Secondary malignant neoplasm of cervix uteri
B58y211	Secondary cancer of the cervix
B58y300	Secondary malignant neoplasm of vagina
B58y400	Secondary malignant neoplasm of vulva
B58y500	Secondary malignant neoplasm of prostate
B58y600	Secondary malignant neoplasm of testis
B58y700	Secondary malignant neoplasm of penis
B58y900	Secondary malignant neoplasm of tongue
B58yz00	Secondary malignant neoplasm of other specified site NOS
B58z.00	Secondary malignant neoplasm of other specified site NOS
B59..00	Malignant neoplasm of unspecified site
B590.00	Disseminated malignancy NOS
B590.11	Carcinomatosis
B591.00	Other malignant neoplasm NOS
B592.00	Malignant neoplasms of independent (primary) multiple sites
B592X00	Kaposi's sarcoma of multiple organs
B593.00	Primary malignant neoplasm of unknown site
B594.00	Secondary malignant neoplasm of unknown site
B59z.00	Malignant neoplasm of unspecified site NOS
B59zX00	Kaposi's sarcoma, unspecified
B5y..00	Malignant neoplasm of other and unspecified site OS
B5z..00	Malignant neoplasm of other and unspecified site NOS
B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
B6...11	Malignant neoplasm of histiocytic tissue
B60..00	Lymphosarcoma and reticulosarcoma
B600.00	Reticulosarcoma
B600000	Reticulosarcoma of unspecified site
B600100	Reticulosarcoma of lymph nodes of head, face and neck
B600300	Reticulosarcoma of intra-abdominal lymph nodes
B601.00	Lymphosarcoma
B601000	Lymphosarcoma of unspecified site
B601100	Lymphosarcoma of lymph nodes of head, face and neck
B601200	Lymphosarcoma of intrathoracic lymph nodes
B601300	Lymphosarcoma of intra-abdominal lymph nodes
B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
B601z00	Lymphosarcoma NOS
B602.00	Burkitt's lymphoma
B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
B602z00	Burkitt's lymphoma NOS
B61..00	Hodgkin's disease
B610.00	Hodgkin's paragranuloma
B611.00	Hodgkin's granuloma

B612.00	Hodgkin's sarcoma
B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance
B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
B614.00	Hodgkin's disease, nodular sclerosis
B614000	Hodgkin's disease, nodular sclerosis of unspecified site
B614100	Hodgkin's nodular sclerosis of head, face and neck
B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
B614z00	Hodgkin's disease, nodular sclerosis NOS
B615.00	Hodgkin's disease, mixed cellularity
B615z00	Hodgkin's disease, mixed cellularity NOS
B616.00	Hodgkin's disease, lymphocytic depletion
B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
B616z00	Hodgkin's disease, lymphocytic depletion NOS
B61z.00	Hodgkin's disease NOS
B61z000	Hodgkin's disease NOS, unspecified site
B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
B61zz00	Hodgkin's disease NOS
B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
B620.00	Nodular lymphoma (Brill - Symmers disease)
B620000	Nodular lymphoma of unspecified site
B620100	Nodular lymphoma of lymph nodes of head, face and neck
B620300	Nodular lymphoma of intra-abdominal lymph nodes
B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
B620800	Nodular lymphoma of lymph nodes of multiple sites
B620z00	Nodular lymphoma NOS
B621.00	Mycosis fungoides
B621000	Mycosis fungoides of unspecified site
B621300	Mycosis fungoides of intra-abdominal lymph nodes
B621500	Mycosis fungoides of lymph nodes of inguinal region and leg
B621z00	Mycosis fungoides NOS
B622.00	Sezary's disease
B623.00	Malignant histiocytosis
B623000	Malignant histiocytosis of unspecified site
B623300	Malignant histiocytosis of intra-abdominal lymph nodes
B623z00	Malignant histiocytosis NOS
B624.00	Leukaemic reticuloendotheliosis
B624.11	Leukaemic reticuloendotheliosis
B624.12	Hairy cell leukaemia
B624000	Leukaemic reticuloendotheliosis of unspecified sites
B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
B625.00	Letterer-Siwe disease
B625.11	Histiocytosis X (acute, progressive)
B625200	Letterer-Siwe disease of intrathoracic lymph nodes
B625800	Letterer-Siwe disease of lymph nodes of multiple sites
B625z00	Letterer-Siwe disease NOS
B626.00	Malignant mast cell tumours
B626800	Mast cell malignancy of lymph nodes of multiple sites
B626z00	Malignant mast cell tumour NOS
B627.00	Non - Hodgkin's lymphoma
B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma

B627200	Follicular non-Hodgkin's large cell lymphoma
B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
B627B00	Other types of follicular non-Hodgkin's lymphoma
B627C00	Follicular non-Hodgkin's lymphoma
B627C11	Follicular lymphoma NOS
B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
B627W00	Unspecified B-cell non-Hodgkin's lymphoma
B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
B62x.00	Malignant lymphoma otherwise specified
B62x100	Lymphoepithelioid lymphoma
B62x200	Peripheral T-cell lymphoma
B62x400	Malignant reticulosis
B62x500	Malignant immunoproliferative small intestinal disease
B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
B62y.00	Malignant lymphoma NOS
B62y000	Malignant lymphoma NOS of unspecified site
B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
B62y700	Malignant lymphoma NOS of spleen
B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
B62yz00	Malignant lymphoma NOS
B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
B62zz11	Immunoproliferative neoplasm
B63..00	Multiple myeloma and immunoproliferative neoplasms
B630.00	Multiple myeloma
B630.11	Kahler's disease
B630.12	Myelomatosis
B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
B630100	Solitary myeloma
B630200	Plasmacytoma NOS
B630300	Lambda light chain myeloma
B631.00	Plasma cell leukaemia
B63y.00	Other immunoproliferative neoplasms
B63z.00	Immunoproliferative neoplasm or myeloma NOS
B64..00	Lymphoid leukaemia
B64..11	Lymphatic leukaemia
B640.00	Acute lymphoid leukaemia
B641.00	Chronic lymphoid leukaemia
B641.11	Chronic lymphatic leukaemia
B642.00	Subacute lymphoid leukaemia
B64y.00	Other lymphoid leukaemia
B64y100	Prolymphocytic leukaemia
B64y200	Adult T-cell leukaemia
B64yz00	Other lymphoid leukaemia NOS
medcode	description
B64z.00	Lymphoid leukaemia NOS
B65..00	Myeloid leukaemia

B650.00	Acute myeloid leukaemia
B651.00	Chronic myeloid leukaemia
B651.11	Chronic granulocytic leukaemia
B651000	Chronic eosinophilic leukaemia
B651z00	Chronic myeloid leukaemia NOS
B652.00	Subacute myeloid leukaemia
B653.00	Myeloid sarcoma
B653000	Chloroma
B65y000	Aleukaemic myeloid leukaemia
B65y100	Acute promyelocytic leukaemia
B65yz00	Other myeloid leukaemia NOS
B65z.00	Myeloid leukaemia NOS
B66..00	Monocytic leukaemia
B66..11	Histiocytic leukaemia
B66..12	Monoblastic leukaemia
B660.00	Acute monocytic leukaemia
B661.00	Chronic monocytic leukaemia
B66z.00	Monocytic leukaemia NOS
B67..00	Other specified leukaemia
B670.00	Acute erythraemia and erythroleukaemia
B670.11	Di Guglielmo's disease
B671.00	Chronic erythraemia
B671.11	Heilmeyer - Schoner disease
B672.11	Thrombocytic leukaemia
B673.00	Mast cell leukaemia
B675.00	Acute myelofibrosis
B67y.00	Other and unspecified leukaemia
B67z.00	Other specified leukaemia NOS
B68..00	Leukaemia of unspecified cell type
B680.00	Acute leukaemia NOS
B681.00	Chronic leukaemia NOS
B68y.00	Other leukaemia of unspecified cell type
B68z.00	Leukaemia NOS
B69..00	Myelomonocytic leukaemia
B690.00	Acute myelomonocytic leukaemia
B691.00	Chronic myelomonocytic leukaemia
B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
B6y0.00	Myeloproliferative disorder
B6y0.11	Myeloproliferative disease
B6y1.00	Myelosclerosis with myeloid metaplasia
B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
B6z0.00	Kaposi's sarcoma of lymph nodes
B8...00	Carcinoma in situ
B8...11	Bowen's disease
B8...12	Erythroplasia
B8...13	Queyrats's erythroplasia
B80..00	Carcinoma in situ of digestive organs
B80..11	Ca-in-situ of G.I. tract
B800.11	Carcinoma in situ of oral cavity
B800.12	Carcinoma in situ of pharynx
B800000	Carcinoma in situ of lip
B800100	Carcinoma in situ of tongue
B800200	Carcinoma in situ of salivary glands
B800300	Carcinoma in situ of gums
B800400	Carcinoma in situ of floor of mouth
B800500	Carcinoma in situ of cheek
B800600	Carcinoma in situ of palate
B800700	Carcinoma in situ of nasopharynx

B800800	Carcinoma in situ of oropharynx
B800900	Carcinoma in situ of hypopharynx
B800z00	Carcinoma in situ of lip, oral cavity and pharynx NOS
B801.00	Carcinoma in situ of oesophagus
B801100	Carcinoma in situ of middle 1/3 oesophagus
B801200	Carcinoma in situ of lower 1/3 oesophagus
B801z00	Carcinoma in situ of oesophagus NOS
B802.00	Carcinoma in situ of stomach
B802000	Carcinoma in situ of cardia of stomach
B802200	Carcinoma in situ of body of stomach
B802300	Carcinoma in situ of pyloric antrum
B802400	Carcinoma in situ of pyloric canal
B802z00	Carcinoma in situ of stomach NOS
B803.00	Carcinoma in situ of colon
B803000	Carcinoma in situ of hepatic flexure of colon
B803100	Carcinoma in situ of transverse colon
B803200	Carcinoma in situ of descending colon
B803300	Carcinoma in situ of sigmoid colon
B803400	Carcinoma in situ of caecum
B803500	Carcinoma in situ of appendix
B803600	Carcinoma in situ of ascending colon
B803700	Carcinoma in situ of splenic flexure of colon
B803z00	Carcinoma in situ of colon NOS
B804.00	Carcinoma in situ of rectum and rectosigmoid junction
B804000	Carcinoma in situ of rectosigmoid junction
B804100	Carcinoma in situ of rectum
B804z00	Carcinoma in situ of rectum or rectosigmoid junction NOS
B805.00	Carcinoma in situ of anal canal
B805000	Anal intraepithelial neoplasia grade III
B806.00	Carcinoma in situ of anus NOS
B807.00	Carcinoma in situ of other and unspecified small intestine
B807000	Carcinoma in situ of duodenum
B807100	Carcinoma in situ of jejunum
B807200	Carcinoma in situ of ileum
B807z00	Carcinoma in situ other and unspecified small intestine NOS
B808.11	Carcinoma in situ of biliary system
B808000	Carcinoma in situ of liver
B808100	Carcinoma in situ of intrahepatic bile ducts
B808200	Carcinoma in situ of hepatic duct
B808300	Carcinoma in situ of gall bladder
B808400	Carcinoma in situ of cystic duct
B808500	Carcinoma in situ of common bile duct
B808600	Carcinoma in situ of ampulla of Vater
B808700	Carcinoma in situ of sphincter of Oddi
B808z00	Carcinoma in situ of liver or biliary system NOS
B80z000	Carcinoma in situ of pancreas
B80z100	Carcinoma in situ of spleen
B81..00	Carcinoma in situ of respiratory system
B810.00	Carcinoma in situ of larynx
B810000	Carcinoma in situ of thyroid cartilage
B810100	Carcinoma in situ of cricoid cartilage
B810200	Carcinoma in situ of epiglottis
B810600	Carcinoma in situ of aryepiglottic fold
B810700	Carcinoma in situ of vestibular fold
B810800	Carcinoma in situ of vocal fold - glottis
B810811	Carcinoma in situ of glottis
B810z00	Carcinoma in situ of larynx NOS
B811.00	Carcinoma in situ of trachea

B812.00	Carcinoma in situ of bronchus and lung
B812000	Carcinoma in situ of carina of bronchus
B812100	Carcinoma in situ of main bronchus
B812200	Carcinoma in situ of upper lobe bronchus and lung
B812300	Carcinoma in situ of middle lobe bronchus and lung
B812400	Carcinoma in situ of lower lobe bronchus and lung
B812z00	Carcinoma in situ of bronchus or lung NOS
B81y.00	Carcinoma in situ of other specified part respiratory system
B81y.11	Carcinoma in situ of nasal sinuses
B81y000	Carcinoma in situ of pleura
B81y100	Carcinoma in situ of nasal cavity
B81y400	Carcinoma in situ of Eustachian tube
B81y600	Carcinoma in situ of maxillary sinus
B81y700	Carcinoma in situ of ethmoidal sinus
B81y900	Carcinoma in situ of sphenoidal sinus
B81z.00	Carcinoma in situ of respiratory organ NOS
B82..00	Carcinoma in situ of skin
B820.00	Carcinoma in situ of skin of lip
B821.00	Carcinoma in situ of skin of eyelid including canthus
B822.00	Carcinoma in situ skin of ear and external auricular canal
B822.11	Carcinoma in situ of ear
B822000	Carcinoma in situ of skin of auricle
B822z00	Carcinoma in situ skin of ear/external auricular canal NOS
B823.00	Carcinoma in situ of skin of other parts of face
B823000	Carcinoma in situ of skin of forehead skin
B823100	Carcinoma in situ of skin of eyebrow
B823300	Carcinoma in situ of skin of cheek
B823400	Carcinoma in situ of skin of nose
B823500	Carcinoma in situ of skin of temple
B823600	Carcinoma in situ of skin of jaw
B823z00	Carcinoma in situ of skin of other parts of face NOS
B824.00	Carcinoma in situ of scalp and skin of neck
B824000	Carcinoma in situ of scalp
B824100	Carcinoma in situ of skin of neck
B825.00	Carcinoma in situ of skin of trunk, excluding scrotum
B825000	Carcinoma in situ of skin of breast
B825100	Carcinoma in situ of skin of chest wall NOS
B825200	Carcinoma in situ of skin of axilla
B825300	Carcinoma in situ of skin of back
B825400	Carcinoma in situ of skin of abdominal wall
B825500	Carcinoma in situ of skin of groin
B825600	Carcinoma in situ of skin of perineum
B825800	Carcinoma in situ of perianal skin
B825z00	Carcinoma in situ of skin of trunk NOS
B826.00	Carcinoma in situ of skin of upper limb and shoulder
B826000	Carcinoma in situ of skin of shoulder
B826100	Carcinoma in situ of skin of upper arm
B826200	Carcinoma in situ of skin of lower arm
B826300	Carcinoma in situ of skin of hand
B826z00	Carcinoma in situ of skin of upper limb or shoulder NOS
B827.00	Carcinoma in situ of skin of lower limb and hip
B827.11	Carcinoma in situ of skin of leg
B827000	Carcinoma in situ of skin of hip
B827100	Carcinoma in situ of skin of thigh
B827200	Carcinoma in situ of skin of knee
B827300	Carcinoma in situ of skin of lower leg
B827400	Carcinoma in situ of skin of foot
B827z00	Carcinoma in situ of skin of lower limb or hip NOS

B828.00	Melanoma in situ of skin
B828000	Melanoma in situ of lip
B828100	Melanoma in situ of eyelid, including canthus
B828300	Melanoma in situ of scalp and neck
B828400	Melanoma in situ of trunk
B828500	Melanoma in situ of upper limb, including shoulder
B828600	Melanoma in situ of lower limb, including hip
B828700	Melanoma in situ of scalp
B828800	Melanoma in situ of back of hand
B828900	Melanoma in situ of back
B828W00	Melanoma in situ, unspecified
B828X00	Melanoma in situ of other and unspecified parts of face
B82y.00	Carcinoma in situ of other specified sites of skin
B82z.00	Carcinoma in situ of skin NOS
B83..00	Carcinoma in situ of breast and genitourinary system
B830.00	Carcinoma in situ of breast
B830000	Lobular carcinoma in situ of breast
B830100	Intraductal carcinoma in situ of breast
B831.00	Carcinoma in situ of cervix uteri
B831.11	CIN III - carcinoma in situ of cervix
B831.12	Cervical intraepithelial neoplasia
B831.13	Cervical intraepithelial neoplasia grade III
B831000	Carcinoma in situ of endocervix
B831100	Carcinoma in situ of exocervix
B832.00	Carcinoma in situ of other and unspecified parts of uterus
B832.11	Carcinoma in situ of body of uterus
B832000	Carcinoma in situ of endometrium
B833.00	Carcinoma in situ other and unspecified female genital organ
B833000	Carcinoma in situ of ovary
B833100	Carcinoma in situ of fallopian tube
B833200	Carcinoma in situ of vagina
B833300	Carcinoma in situ of vulva
B833311	Vulval intraepithelial neoplasia
B833z00	Carcinoma in situ of female genital organs NOS
B834.00	Carcinoma in situ of prostate
B834000	High grade prostatic intraepithelial neoplasia
B835.00	Carcinoma in situ of penis
B836000	Carcinoma in situ of testis
B836300	Carcinoma in situ of scrotum
B837.00	Carcinoma in situ of bladder
B83z.00	Carcinoma in situ of urinary organs NOS
B8y..00	Carcinoma in situ of other and unspecified sites
B8y0.00	Carcinoma in situ of eye
B8yy.00	Carcinoma in situ of other specified site
B8yy000	Carcinoma in situ of thyroid gland
B8yy100	Carcinoma in situ of adrenal gland
B8yy200	Carcinoma in situ of parathyroid gland
B8yy300	Carcinoma in situ of pituitary gland
B8yyz00	Carcinoma in situ of other specified site NOS
B8z..00	Carcinoma in situ NOS
B9...00	Neoplasms of uncertain behaviour
B90..00	Neop uncertain behaviour of digestive and respiratory system
B900.00	Neoplasm of uncertain behaviour of major salivary glands
B900000	Neoplasm of uncertain behaviour of parotid gland
B900011	Mixed parotid tumour
B900200	Neoplasm of uncertain behaviour of submandibular gland
B901.11	Neoplasm of uncertain behaviour of oral cavity
B901.12	Neoplasm of uncertain behaviour of pharynx

B901000	Neoplasm of uncertain behaviour of lip
B901100	Neoplasm of uncertain behaviour of tongue
B901300	Neoplasm of uncertain behaviour of gums
B901400	Neoplasm of uncertain behaviour of floor of mouth
B901500	Neoplasm of uncertain behaviour of cheek
B901600	Neoplasm of uncertain behaviour of palate
B901700	Neoplasm of uncertain behaviour of nasopharynx
B901800	Neoplasm of uncertain behaviour of oropharynx
B901900	Neoplasm of uncertain behaviour of hypopharynx
B902000	Neoplasm of uncertain behaviour of stomach
B902100	Neoplasm of uncertain behaviour of duodenum
B902400	Neoplasm of uncertain behaviour of colon
B902500	Neoplasm of uncertain behaviour of rectum
B902600	Neoplasm of uncertain or unknown behaviour of appendix
B903.00	Neoplasm of uncertain behaviour of liver and biliary passage
B903.11	Neoplasm of uncertain behaviour of biliary system
B903000	Neoplasm of uncertain behaviour of liver
B903300	Neoplasm of uncertain behaviour of gall bladder
B903700	Neoplasm of uncertain behaviour of sphincter of Oddi
B904000	Neoplasm of uncertain behaviour of retroperitoneum
B904100	Neoplasm of uncertain behaviour of peritoneum
B905000	Neoplasm of uncertain behaviour of oesophagus
B905100	Neoplasm of uncertain behaviour of pancreas
B905200	Neoplasm of uncertain behaviour of anal canal and sphincter
B905300	Neoplasm of uncertain behaviour of spleen
B906.00	Neoplasm of uncertain behaviour of larynx
B906000	Neoplasm of uncertain behaviour of thyroid cartilage
B906200	Neoplasm of uncertain behaviour of epiglottis
B906600	Neoplasm of uncertain behaviour of aryepiglottic fold
B906800	Neoplasm of uncertain behaviour of vocal cord
B907.00	Neoplasm of uncertain behaviour trachea, bronchus and lung
B907000	Neoplasm of uncertain behaviour of trachea
B907100	Neoplasm of uncertain behaviour of bronchus
B907200	Neoplasm of uncertain behaviour of lung
B908000	Neoplasm of uncertain behaviour of pleura
B908100	Neoplasm of uncertain behaviour of thymus
B908200	Neoplasm of uncertain behaviour of mediastinum
B90z100	Neoplasm of uncertain behaviour of tympanic cavity
B90z400	Neoplasm of uncertain behaviour of mastoid air cells
B90z500	Neoplasm of uncertain behaviour of maxillary sinus
B90z600	Neoplasm of uncertain behaviour of ethmoidal sinus
B91..00	Neoplasm of uncertain behaviour of genitourinary organs
B910.00	Neoplasm of uncertain behaviour of uterus
B911000	Malignant hydatidiform mole
B911013	Choriocarcinoma
B912.00	Neoplasm of uncertain behaviour of ovary
B913.00	Neoplasm of uncertain behaviour other female genital organs
B913000	Neoplasm of uncertain behaviour of vagina
B913100	Neoplasm of uncertain behaviour of vulva
B914.00	Neoplasm of uncertain behaviour of testis
B915.00	Neoplasm of uncertain behaviour of prostate
B916000	Neoplasm of uncertain behaviour of penis
B916100	Neoplasm of uncertain behaviour of epididymis
B916200	Neoplasm of uncertain behaviour of scrotum
B917.00	Neoplasm of uncertain behaviour of bladder
B917.12	Transitional cell papilloma of bladder
B91z.11	Neoplasm of uncertain behaviour of urinary organ NOS
B91z100	Neoplasm of uncertain behaviour of kidney

B91z111	Renal neoplasm of uncertain behaviour
B91z200	Uncertain neoplasm ureter
B91z300	Neoplasm of uncertain or unknown behaviour of renal pelvis
B92..00	Neop of uncertain behaviour of endocrine and nervous system
B920.00	Neop uncertain behaviour pituitary and craniopharyngeal duct
B920000	Neoplasm of uncertain behaviour of pituitary gland
B920100	Neoplasm of uncertain behaviour of craniopharyngeal duct
B920z00	Neop uncertain behaviour pituitary and craniopharyngeal NOS
B921.00	Neoplasm of uncertain behaviour of pineal gland
B922.00	Neoplasm of uncertain behaviour of adrenal gland
B923000	Neoplasm of uncertain behaviour of carotid body
B923100	Neoplasm of uncertain behaviour of glomus jugulare
B923300	Neoplasm of uncertain behaviour of coccygeal body
B923z00	Neoplasm of uncertain behaviour of paraganglia NOS
B924000	Neoplasm of uncertain behaviour of thyroid gland
B924100	Neoplasm of uncertain behaviour of parathyroid gland
B924z00	Neoplasm of uncertain behaviour of endocrine gland NOS
B925000	Neoplasm of uncertain behaviour of brain
B925100	Neoplasm of uncertain behaviour of spinal cord
B925200	Neoplasm of uncertain or unknown behav brain, supratentorial
B926.00	Neoplasm of uncertain behaviour of meninges
B927.00	Neurofibromatosis - Von Recklinghausen's disease
B927.11	Von Recklinghausen's disease
B928.00	Neopl uncert/unkn behav of periph nerves & autonom nerv sys
B92z.00	Neoplasm of uncertain behaviour of nervous system OS/NOS
B93..00	Neop uncertain behaviour other and unspec sites and tissues
B932.00	Neoplasm of uncertain behaviour of skin
B933.00	Neoplasm of uncertain behaviour of breast
B933.11	Cystosarcoma phyllodes
B934.00	Polycythaemia vera
B934.11	Polycythaemia rubra vera
B934.12	Primary polycythaemia
B935.00	Neoplasm of uncertain behaviour of histiocytic and mast cell
B935.11	Histiocytic tumour NOS
B935.12	Mastocytoma NOS
B936.00	Neoplasm of uncertain behaviour of plasma cells
B936.11	Myeloma - solitary
B936.12	Plasmacytoma NOS
B937.00	Neop uncertain behaviour other lymphatic/haematopoietic tiss
B937.12	Idiopathic thrombocythaemia
B937.14	Myelodysplasia
B93X.00	Neo/uncertn+unknwn behav/lymph,h'matopetc+rel tiss,unspcf
B93y000	Neoplasm of uncertain behaviour of eye
B93y100	Neoplasm of uncertain behaviour of heart
B93yz00	Neop of uncertain behaviour of other specified sites NOS
B93z.00	Neop uncertain behaviour other unspec site and tissue NOS
B9y..00	Neoplasm of uncertain behaviour otherwise specified
B9z..00	Neoplasm of uncertain behaviour NOS
BA...00	Unspecified nature neoplasm
BA0..00	Neoplasm of unspecified nature
BA00.00	Neoplasm of unspecified nature of digestive system
BA01.00	Neoplasm of unspecified nature of respiratory system
BA02.00	Neoplasm of unspecified nature of bone, skin and soft tissue
BA02000	Neoplasm of unspecified nature of bone
BA02200	Neoplasm of unspecified nature of skin
BA02z00	Neoplasm of unspec nature of bone, skin or soft tissue NOS
BA03.00	Neoplasm of unspecified nature of breast
BA04.00	Neoplasm of unspecified nature of bladder

BA05.00	Neoplasm of unspecified nature of other genitourinary organs
BA06.00	Neoplasm of unspecified nature of brain
BA07.00	Neop unspec nature of endocrine glands, other nervous system
BA0y.00	Neoplasm of unspecified nature of other specified sites
BA0z.00	Neoplasm of unspecified nature NOS
BAz..00	Neoplasm of unspecified nature NOS
BB...00	[M]Morphology of neoplasms
BB...11	[M]Tumour morphology
BB0..00	[M]Neoplasms NOS
BB02.00	[M]Neoplasm, malignant
BB03.00	[M]Neoplasm, metastatic
BB03.11	[M]Secondary neoplasm
BB03.13	[M]Tumour embolism
BB04.00	[M]Neoplasm, malig, uncertain whether primary or metastatic
BB07.00	[M]Tumour cells, malignant
BB08.00	[M]Malignant tumour, small cell type
BB09.00	[M]Malignant tumour, giant cell type
BB0A.00	[M]Malignant tumour, fusiform cell type
BB0z.00	[M]Unspecified tumour cell NOS
BB1..00	[M]Epithelial neoplasms NOS
BB11.00	[M]Carcinoma in situ NOS
BB11.11	[M]Intraepithelial carcinoma NOS
BB12.00	[M]Carcinoma NOS
BB13.00	[M]Carcinoma, metastatic, NOS
BB13.11	[M]Secondary carcinoma
BB14.00	[M]Carcinomatosis
BB16.00	[M]Epithelioma, malignant
BB17.00	[M]Large cell carcinoma NOS
BB18.00	[M]Carcinoma, undifferentiated type, NOS
BB19.00	[M]Carcinoma, anaplastic type, NOS
BB1A.00	[M]Pleomorphic carcinoma
BB1B.00	[M]Giant cell and spindle cell carcinoma
BB1C.00	[M]Giant cell carcinoma
BB1D.00	[M]Spindle cell carcinoma
BB1E.00	[M]Pseudosarcomatous carcinoma
BB1F.00	[M]Polygonal cell carcinoma
BB1G.00	[M]Spheroidal cell carcinoma
BB1H.00	[M]Tumourlet
BB1J.00	[M]Small cell carcinoma NOS
BB1J.12	[M]Round cell carcinoma
BB1K.00	[M]Oat cell carcinoma
BB1L.00	[M]Small cell carcinoma, fusiform cell type
BB1M.00	[M]Small cell carcinoma, intermediate cell
BB1N.00	[M]Small cell-large cell carcinoma
BB1z.00	[M]Unspecified epithelial neoplasm
BB2..00	[M]Papillary and squamous cell neoplasms
BB2..11	[M]Papillary neoplasms
BB2..12	[M]Squamous cell neoplasms
BB20.00	[M]Papilloma NOS (excluding papilloma of urinary bladder)
BB21.00	[M]Papillary carcinoma in situ
BB22.00	[M]Papillary carcinoma NOS
BB23.00	[M]Verrucous papilloma
BB24.00	[M]Verrucous carcinoma NOS
BB24.11	[M]Verrucous epidermoid carcinoma
BB24.12	[M]Verrucous squamous cell carcinoma
BB25.00	[M]Squamous cell papilloma
BB25.11	[M]Dyskeratotic papilloma
BB25.12	[M]Hyperkeratotic papilloma

BB25.13	[M]Keratotic papilloma
BB25.14	[M]Parakeratotic papilloma
BB26.00	[M]Papillary squamous cell carcinoma
BB26.11	[M]Papillary epidermoid carcinoma
BB27.00	[M]Inverted papilloma
BB28.00	[M]Papillomatosis NOS
BB29.00	[M]Squamous cell carcinoma in situ NOS
BB29.11	[M]Epidermoid carcinoma in situ
BB29.12	[M]Intraepidermal carcinoma NOS
BB29.13	[M]Intraepithelial squamous cell carcinoma
BB2A.00	[M]Squamous cell carcinoma NOS
BB2A.11	[M]Epidermoid carcinoma NOS
BB2A.13	[M]Squamous cell carcinoma of skin NOS
BB2B.00	[M]Squamous cell carcinoma, metastatic NOS
BB2C.00	[M]Squamous cell carcinoma, keratinising type NOS
BB2C.11	[M]Epidermoid carcinoma, keratinising type
BB2E.00	[M]Squamous cell carcinoma, small cell, non-keratinising
BB2F.00	[M]Squamous cell carcinoma, spindle cell type
BB2G.00	[M]Adenoid squamous cell carcinoma
BB2H.00	[M]Squamous cell ca-in-situ, questionable stromal invasion
BB2J.00	[M]Squamous cell carcinoma, microinvasive
BB2K.00	[M]Queyrat's erythroplasia
BB2L.00	[M]Bowen's disease
BB2M.00	[M]Lymphoepithelial carcinoma
BB2N.00	[M]Intraepit neop,grade III,of cervix, vulva and vagina
BB2z.00	[M]Papillary or squamous cell neoplasm NOS
BB3..00	[M]Basal cell neoplasms
BB30.00	[M]Basal cell tumour
BB31.00	[M]Basal cell carcinoma NOS
BB32.00	[M]Multicentric basal cell carcinoma
BB33.00	[M]Basal cell carcinoma, morphoea type
BB34.00	[M]Basal cell carcinoma, fibroepithelial type
BB35.00	[M]Basosquamous carcinoma
BB36.00	[M]Metatypical carcinoma
BB37.00	[M]Intraepidermal epithelioma of Jadassohn
BB38.00	[M]Trichoepithelioma
BB38.12	[M]Epithelioma adenoides cyst
BB39.00	[M]Trichofolliculoma
BB3A.00	[M]Tricholemmoma
BB3B.00	[M]Pilomatrixoma
BB3B.11	[M]Malherbe's calcified epithelioma
BB3z.00	[M]Basal cell neoplasm NOS
BB4..00	[M]Transitional cell papillomas and carcinomas
BB40.00	[M]Transitional cell papilloma NOS
BB41.00	[M]Urothelial papilloma
BB41.11	[M]Urinary bladder papilloma
BB42.00	[M]Transitional cell carcinoma in situ
BB43.00	[M]Transitional cell carcinoma NOS
BB43.11	[M]Urothelial carcinoma
BB44.00	[M]Schneiderian papilloma
BB45.00	[M]Transitional cell papilloma, inverted type
BB47.00	[M]Transitional cell carcinoma, spindle cell type
BB48.00	[M]Basaloid carcinoma
BB49.00	[M]Cloacogenic carcinoma
BB4A.00	[M]Papillary transitional cell carcinoma
BB4z.00	[M]Transitional cell papilloma or carcinoma NOS
BB5..00	[M]Adenomas and adenocarcinomas
BB5..11	[M]Adenocarcinomas

BB5..12	[M]Adenomas
BB50.00	[M]Adenoma NOS
BB50000	[M]Microcystic adenoma
BB51.00	[M]Adenocarcinoma in situ
BB51000	[M]Adenocarcinoma in situ in villous adenoma
BB51100	[M]Adenocarcinoma in situ in tubulovillous adenoma
BB52.00	[M]Adenocarcinoma NOS
BB52000	[M]Adenocarcinoma in tubulovillous adenoma
BB53.00	[M]Adenocarcinoma, metastatic, NOS
BB54.00	[M]Scirrhous adenocarcinoma
BB55.00	[M]Linitis plastica
BB56.00	[M]Superficial spreading adenocarcinoma
BB57.00	[M]Adenocarcinoma, intestinal type
BB58.00	[M]Carcinoma, diffuse type
BB59.00	[M]Monomorphic adenoma
BB5A.00	[M]Basal cell adenoma
BB5B.00	[M]Pancreatic adenomas and carcinomas
BB5B000	[M]Islet cell adenoma
BB5B011	[M]Nesidioblastoma
BB5B100	[M]Islet cell carcinoma
BB5B200	[M]Insulinoma NOS
BB5B400	[M]Glucagonoma NOS
BB5B500	[M]Glucagonoma, malignant
BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
BB5C.00	[M]Gastrinoma and carcinomas
BB5C000	[M]Gastrinoma NOS
BB5C011	[M]G cell tumour NOS
BB5C100	[M]Gastrinoma, malignant
BB5Cz00	[M]Gastrinoma or carcinoma NOS
BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
BB5D011	[M]Cholangioma
BB5D100	[M]Cholangiocarcinoma
BB5D111	[M]Bile duct carcinoma
medcode	description
BB5D200	[M]Bile duct cystadenoma
BB5D300	[M]Bile duct cystadenocarcinoma
BB5D400	[M]Liver cell adenoma
BB5D411	[M]Hepatocellular adenoma
BB5D500	[M]Hepatocellular carcinoma NOS
BB5D511	[M]Hepatoma NOS
BB5D512	[M]Hepatoma, malignant
BB5D513	[M]Liver cell carcinoma
BB5D800	[M]Hepatocellular carcinoma, fibrolamellar
BB5Dz00	[M]Hepatobiliary adenoma or carcinoma NOS
BB5E.00	[M]Trabecular adenoma
BB5H.00	[M]Eccrine dermal cylindroma
BB5H.11	[M]Turban tumour
BB5J.00	[M]Adenoid cystic carcinoma
BB5J.11	[M]Cylindroid adenocarcinoma
BB5J.12	[M]Cylindroid bronchial adenoma
BB5J.13	[M]Cylindroma NOS
BB5K.00	[M]Cribriform carcinoma
BB5L.00	[M]Adenomatous and adenocarcinomatous polyps
BB5L000	[M]Adenomatous polyp NOS
BB5L011	[M]Polypoid adenoma
BB5L100	[M]Adenocarcinoma in adenomatous polyp
BB5L200	[M]Adenocarcinoma in situ in adenomatous polyp

BB5L300	[M]Adenocarcinoma in multiple adenomatous polyps
BB5Lz00	[M]Adenomatous or adenocarcinomatous polyp NOS
BB5M.00	[M]Tubular adenomas and adenocarcinomas
BB5M000	[M]Tubular adenoma NOS
BB5M100	[M]Tubular adenocarcinoma
BB5Mz00	[M]Tubular adenoma or adenocarcinoma NOS
BB5N.00	[M]Adenomatous and adenocarcinomatous polyps of colon
BB5N.11	[M]Adenoma or or adenocarcinoma in polyposis coli
BB5N000	[M]Adenomatous polyposis coli
BB5N011	[M]Adenomatosis NOS
BB5N012	[M]Familial polyposis coli
BB5N200	[M]Multiple adenomatous polyps
BB5N211	[M]Multiple polyposis
BB5Nz00	[M]Adenomatous or adenocarcinomatous polyps of the colon NOS
BB5P.00	[M]Solid carcinoma NOS
BB5R.00	[M]Carcinoid tumours
BB5R000	[M]Carcinoid tumour NOS
BB5R100	[M]Carcinoid tumour, malignant
BB5R111	[M]Carcinoid bronchial adenoma
BB5R200	[M]Carcinoid tumour, argentaffin, NOS
BB5R211	[M]Argentaffinoma NOS
BB5R600	[M]Mucocarcinoid tumour, malignant
BB5R611	[M]Goblet cell tumour
BB5R800	[M]Adenocarcinoid tumour
BB5R900	[M]Neuroendocrine carcinoma
BB5RA00	[M]Merkel cell carcinoma
BB5Rz00	[M]Carcinoid tumours NOS
BB5S.00	[M]Respiratory tract adenomas and adenocarcinomas
BB5S000	[M]Pulmonary adenomatosis
BB5S100	[M]Bronchial adenoma NOS
BB5S200	[M]Bronchiolo-alveolar adenocarcinoma
BB5S211	[M]Alveolar cell carcinoma
BB5S212	[M]Bronchiolar carcinoma
BB5S400	[M]Alveolar adenocarcinoma
BB5Sz00	[M]Respiratory tract adenoma or adenocarcinoma NOS
BB5T.00	[M]Papillary adenomas and adenocarcinomas
BB5T000	[M]Papillary adenoma NOS
BB5T100	[M]Papillary adenocarcinoma NOS
BB5Tz00	[M]Papillary adenoma or adenocarcinoma NOS
BB5U.00	[M]Villous adenomas and adenocarcinomas
BB5U000	[M]Villous adenoma NOS
BB5U011	[M]Villous papilloma
BB5U100	[M]Adenocarcinoma in villous adenoma
BB5U200	[M]Villous adenocarcinoma
BB5U300	[M]Tubulovillous adenoma
BB5U311	[M]Papillotubular adenoma
BB5U312	[M]Villoglandular adenoma
BB5Uz00	[M]Villous adenoma or adenocarcinoma NOS
BB5V.00	[M]Pituitary adenomas and carcinomas
BB5V000	[M]Chromophobe adenoma
BB5V100	[M]Chromophobe carcinoma
BB5V200	[M]Acidophil adenoma
BB5V600	[M]Basophil adenoma
BB5V611	[M]Mucoid cell adenoma
BB5V711	[M]Mucoid cell carcinoma
BB5Vz00	[M]Pituitary adenoma or carcinoma NOS
BB5W.00	[M]Oxyphilic adenomas and adenocarcinomas
BB5W000	[M]Oxyphilic adenoma

BB5W011	[M]Hurthle cell adenoma
BB5W012	[M]Oncocytic adenoma
BB5W013	[M]Oncocytoma
BB5W100	[M]Oxyphilic adenocarcinoma
BB5W111	[M]Hurthle cell adenocarcinoma
BB5X.00	[M]Clear cell adenomas and adenocarcinomas
BB5X000	[M]Clear cell adenoma
BB5X100	[M]Clear cell adenocarcinoma NOS
BB5Xz00	[M]Clear cell adenoma or adenocarcinoma NOS
BB5Y.00	[M]Hypernephroid tumour
BB5Z.00	[M]Clear cell adenofibroma
BB5a.00	[M]Renal adenoma and carcinoma
BB5a000	[M]Renal cell carcinoma
BB5a011	[M]Grawitz tumour
BB5a012	[M]Hypernephroma
BB5az00	[M]Renal adenoma or carcinoma NOS
BB5b.00	[M]Granular cell carcinoma
BB5c.00	[M]Parathyroid adenomas and adenocarcinomas
BB5c000	[M]Chief cell adenoma
BB5cz00	[M]Parathyroid adenoma or adenocarcinoma NOS
BB5e.00	[M]Lipoadenoma
BB5f.00	[M]Thyroid adenoma and adenocarcinoma
BB5f000	[M]Follicular adenoma
BB5f100	[M]Follicular adenocarcinoma NOS
BB5f111	[M]Follicular carcinoma
BB5f200	[M]Follicular adenocarcinoma, well differentiated type
BB5f400	[M]Microfollicular adenoma
BB5f500	[M]Macrofollicular adenoma
BB5f511	[M]Colloid adenoma
BB5f600	[M]Papillary and follicular adenocarcinoma
BB5fz00	[M]Thyroid adenoma or adenocarcinoma NOS
BB5g.00	[M]Multiple endocrine adenomas
BB5h.00	[M]Adrenal cortical tumours
BB5h000	[M]Adrenal cortical adenoma NOS
BB5h100	[M]Adrenal cortical carcinoma
BB5hz00	[M]Adrenal cortical tumours NOS
BB5j.00	[M]Endometrioid adenomas and carcinomas
BB5j000	[M]Endometrioid adenoma NOS
BB5j011	[M]Endometrioid cystadenoma NOS
BB5j100	[M]Endometrioid adenoma, borderline malignancy
BB5j200	[M]Endometrioid carcinoma
BB5jz00	[M]Endometrioid adenoma or carcinoma NOS
BB5y.00	[M]Adenoma and adenocarcinoms OS
BB5y000	[M]Basal cell adenocarcinoma
BB5y100	[M]Vipoma
BB5y200	[M]Klatskin's tumour
BB5y300	[M]Apudoma
BB5y400	[M]Prolactinoma
BB5z.00	[M]Adenoma or adenocarcinoma NOS
BB6..00	[M]Adnexal and skin appendage neoplasms
BB60100	[M]Skin appendage carcinoma
BB61.00	[M]Sweat gland adenoma and adenocarcinomas
BB61000	[M]Sweat gland adenoma
BB61011	[M]Hidradenoma NOS
BB61012	[M]Nodular hidradenoma
BB61013	[M]Syringadenoma NOS
BB61100	[M]Sweat gland tumour NOS
BB61200	[M]Sweat gland adenocarcinoma

BB62.00	[M]Apocrine adenoma and adenocarcinomas
BB62000	[M]Apocrine adenoma
BB63.00	[M]Eccrine acrospiroma
BB63.11	[M]Clear cell hidradenoma
BB63.12	[M]Eccrine poroma
BB64.00	[M]Eccrine spiradenoma
BB64.11	[M]Spiradenoma NOS
BB65.00	[M]Hidrocystoma
BB66.00	[M]Papillary hydradenoma
BB67.00	[M]Papillary syringadenoma
BB68.00	[M]Syringoma NOS
BB69.00	[M]Sebaceous adenoma and adenocarcinoma
BB69000	[M]Sebaceous adenoma
BB69100	[M]Sebaceous adenocarcinoma
BB6A.00	[M]Ceruminous adenoma and adenocarcinoma
BB6A000	[M]Ceruminous adenoma
BB6B.00	[M]Eccrine papillary adenoma
BB6z.00	[M]Adnexal and skin appendage neoplasm NOS
BB7..00	[M]Mucoepidermoid neoplasms
BB70.00	[M]Mucoepidermoid tumour
BB71.00	[M]Mucoepidermoid carcinoma
BB8..00	[M]Cystic, mucinous and serous neoplasms
BB80.00	[M]Cystadenoma and carcinoma
BB80000	[M]Cystadenoma NOS
BB80011	[M]Cystoma NOS
BB80100	[M]Cystadenocarcinoma NOS
BB80200	[M]Borderline mucinous cystadenoma of the ovary
BB81.00	[M]Ovarian cystic, mucinous and serous neoplasms
BB81.11	[M]Ovarian cystadenoma or carcinoma
BB81.12	[M]Ovarian mucinous tumour
BB81.13	[M]Ovarian papillary tumour
BB81.14	[M]Ovarian serous tumour
BB81000	[M]Serous cystadenoma NOS
BB81100	[M]Serous cystadenoma, borderline malignancy
BB81200	[M]Serous cystadenocarcinoma, NOS
BB81300	[M]Papillary cystadenoma NOS
BB81400	[M]Papillary cystadenoma, borderline malignancy
BB81500	[M]Papillary cystadenocarcinoma, NOS
BB81600	[M]Papillary serous cystadenoma NOS
BB81700	[M]Papillary serous cystadenoma, borderline malignancy
BB81800	[M]Papillary serous cystadenocarcinoma
BB81900	[M]Serous surface papilloma NOS
BB81B00	[M]Serous surface papillary carcinoma
BB81C00	[M]Mucinous cystadenoma NOS
BB81C11	[M]Pseudomucinous cystadenoma NOS
BB81D00	[M]Mucinous cystadenoma, borderline malignancy
BB81E00	[M]Mucinous cystadenocarcinoma NOS
BB81E11	[M]Pseudomucinous adenocarcinoma
BB81F00	[M]Papillary mucinous cystadenoma NOS
BB81H00	[M]Papillary mucinous cystadenocarcinoma
BB81J00	[M]Serous cystadenoma, borderline malignancy
BB81K00	[M]Papillary cystadenoma, borderline malignancy
BB81L00	[M]Papillary cystic tumour
BB81M00	[M]Papillary serous cystadenoma, borderline malignancy
BB81z00	[M]Ovarian cystic, mucinous or serous neoplasm NOS
BB82.00	[M]Mucinous adenoma and adenocarcinoma
BB82000	[M]Mucinous adenoma
BB82100	[M]Mucinous adenocarcinoma

BB82113	[M]Mucoid adenocarcionoma
BB82114	[M]Mucous adenocarcinoma
BB82z00	[M]Mucinous adenoma or adenocarcinoma NOS
BB83.00	[M]Pseudomyxoma peritonei
BB84.00	[M]Mucin-producing adenocarcinoma
BB85.00	[M]Signet ring carcinoma
BB85000	[M]Signet ring cell carcinoma
BB85100	[M]Metastatic signet ring cell carcinoma
BB85111	[M]Krukenberg tumour
BB8z.00	[M]Cystic, mucinous or serous neoplasm NOS
BB9..00	[M]Ductal, lobular and medullary neoplasms
BB90.00	[M]Intraductal carcinoma, noninfiltrating NOS
BB91.00	[M]Infiltrating duct carcinoma
BB91.11	[M]Duct carcinoma NOS
BB91000	[M]Intraductal papillary adenocarcinoma with invasion
BB91100	[M]Infiltrating duct and lobular carcinoma
BB93.00	[M]Comedocarcinoma NOS
BB94.00	[M]Juvenile breast carcinoma
BB94.11	[M]Secretory breast carcinoma
BB95.00	[M]Intraductal papilloma
BB95.11	[M]Duct adenoma NOS
BB95.12	[M]Ductal papilloma
BB97.00	[M]Intracystic papillary adenoma
BB99.00	[M]Intraductal papillomatosis NOS
BB9A.00	[M]Subareolar duct papillomatosis
BB9A.11	[M]Adenoma of the nipple
BB9A.12	[M]Erosive nipple adenomatosis
BB9B.00	[M]Medullary carcinoma NOS
BB9B.11	[M]C cell carcinoma
BB9C.00	[M]Medullary carcinoma with amyloid stroma
BB9E.00	[M]Lobular carcinoma in situ
BB9E000	[M]Intraductal carcinoma and lobular carcinoma in situ
BB9F.00	[M]Lobular carcinoma NOS
BB9G.00	[M]Infiltrating ductular carcinoma
BB9H.00	[M]Inflammatory carcinoma
BB9J.00	[M]Paget's disease, mammary
BB9J.11	[M]Paget's disease, breast
BB9K.00	[M]Paget's disease and infiltrating breast duct carcinoma
BB9K000	[M]Paget's disease and intraductal carcinoma of breast
BB9L.00	[M]Paget's disease, extramammary, exc Paget's disease bone
BB9M.00	[M]Intracystic carcinoma NOS
BB9z.00	[M]Ductal, lobular or medullary neoplasm NOS
BBA..00	[M]Acinar cell neoplasms
BBA1.00	[M]Acinar cell tumour
BBA2.00	[M]Acinar cell carcinoma
BBB..00	[M]Complex epithelial neoplasms
BBB0.00	[M]Adenosquamous carcinoma
BBB1.00	[M]Adenolymphoma
BBB1.11	[M]Warthin's tumour
BBB2.00	[M]Adenocarcinoma with squamous metaplasia
BBB2.11	[M]Adenoacanthoma
BBB3.00	[M]Adenocarcinoma with cartilaginous and osseous metaplasia
BBB6.00	[M]Thymoma
BBB6z00	[M]Thymoma NOS
BBBz.00	[M]Complex epithelial neoplasm NOS
BBC..00	[M]Specialised gonadal neoplasms
BBC0.00	[M]Sex cord-stromal tumour
BBC0.11	[M]Gonadal stromal tumour

BBC0.12	[M]Ovarian stromal tumour
BBC0.13	[M]Testicular stromal tumour
BBC0000	[M]Sex cord tumour with annular tubules
BBC1.00	[M]Thecal cell neoplasms
BBC1000	[M]Thecoma NOS
BBC1200	[M]Thecoma, luteinized
BBC1z00	[M]Thecal cell neoplasm NOS
BBC3.00	[M]Granulosa cell tumour NOS
BBC3000	[M]Juvenile granulosa cell tumour
BBC4.00	[M]Granulosa cell tumour, malignant
BBC5.00	[M]Granulosa cell-theca cell tumour
BBC6.00	[M]Androblastoma
BBC6z11	[M]Arrhenoblastoma NOS
BBC7.00	[M]Sertoli-Leydig cell tumour
BBC8.00	[M]Gynandroblastoma
BBC9.00	[M]Tubular androblastoma NOS
BBC9.11	[M]Pick's tubular adenoma
BBC9.13	[M]Sertoli cell tumour
BBC9.14	[M]Testicular adenoma
BBCA.00	[M]Sertoli cell carcinoma
BBCC.00	[M]Leydig cell tumour
BBCD.00	[M]Hilar cell tumour
BBCE.00	[M]Lipid cell tumour of ovary
BBCF.00	[M]Adrenal rest tumour
BBCG.00	[M]Sclerosing stromal tumour
BBD..00	[M]Paragangliomas and glomus tumours
BBD0.00	[M]Paraganglioma NOS
BBD4.00	[M]Glomus jugulare tumour
BBD4.11	[M]Jugular paraganglioma
BBD5.00	[M]Aortic body tumour
BBD6.00	[M]Carotid body tumour
BBD7.00	[M]Extra-adrenal paraganglioma, NOS
BBD7.11	[M]Chemodectoma
BBD9.00	[M]Phaeochromocytoma NOS
BBDA.00	[M]Phaeochromocytoma, malignant
BBDB.00	[M]Glomangiosarcoma
BBDC.00	[M]Glomus tumour
BBDD.00	[M]Glomangioma
BBDE.00	[M]Gangliocytic paraganglioma
BBDF.00	[M]Glomangiomyoma
BBDz.00	[M]Paraganglioma or glomus tumour NOS
BBE..00	[M]Naevi and melanomas
BBE0.00	[M]Pigmented naevus NOS
BBE0.11	[M]Hairy naevus NOS
BBE0.12	[M]Naevus NOS
BBE1.00	[M]Malignant melanoma NOS
BBE1.11	[M]Melanocarcinoma
BBE1.12	[M]Melanoma NOS
BBE1.13	[M]Melanosarcoma NOS
BBE1.14	[M]Naevocarcinoma
BBE1000	[M]Malignant melanoma, regressing
BBE1100	[M]Desmoplastic melanoma, malignant
BBE2.00	[M]Nodular melanoma
BBE5.00	[M]Halo naevus
BBE6.00	[M]Fibrous papule of nose
BBE6.11	[M]Involuting naevus
BBE7.00	[M]Neuronaevus
BBE8.00	[M]Magnocellular naevus

BBE8.11	[M]Melanocytoma of eyeball
BBE9.00	[M]Nonpigmented naevus
BBE9.11	[M]Achromic naevus
BBEA.00	[M]Amelanotic melanoma
BBEB.00	[M]Junctional naevus
BBEB.11	[M]Intraepidermal naevus
BBEC.00	[M]Malignant melanoma in junctional naevus
BBED.00	[M]Precancerous melanosis NOS
BBEF.00	[M]Hutchinson's melanotic freckle
BBEF.11	[M]Lentigo maligna
BBEG.00	[M]Malignant melanoma in Hutchinson's melanotic freckle
BBEG.11	[M]Lentigo maligna melanoma
BBEG000	[M]Acral lentiginous melanoma, malignant
BBEH.00	[M]Superficial spreading melanoma
BBEJ.00	[M]Intradermal naevus
BBEJ.11	[M]Dermal naevus
BBEK.00	[M]Compound naevus
BBEL.00	[M]Giant pigmented naevus
BBEN.00	[M]Epithelioid and spindle cell naevus
BBEN.11	[M]Juvenila melanoma
BBEN.12	[M]Juvenila naevus
BBEN.13	[M] Spitz naevus
BBEQ.00	[M]Spindle cell melanoma NOS
BBET.00	[M]Mixed epithelioid and spindle melanoma
BBEU.00	[M]Blue naevus NOS
BBEU.11	[M]Jadassohn's blue naevus
BBEV.00	[M]Blue naevus, malignant
BBEW.00	[M]Cellular blue naevus
BBEX.00	[M]Melanoma in situ
BBEY.00	[M]Dysplastic naevus
BBEa.00	[M]Spindle cell naevus
BBEb.00	[M] Epithelioid cell naevus
BBEz.00	[M]Naevi or melanoma NOS
BBF..00	[M]Soft tissue tumours and sarcomas NOS
BBF1.00	[M]Sarcoma NOS
BBF2.00	[M]Sarcomatosis NOS
BBF3.00	[M]Spindle cell sarcoma
BBF4.11	[M]Pleomorphic cell sarcoma
BBF5.00	[M]Small cell sarcoma
BBF5.11	[M]Round cell sarcoma
BBF6.00	[M]Epithelioid cell sarcoma
BBFz.00	[M]Soft tissue tumour or sarcoma NOS
BBG..00	[M]Fibromatous neoplasms
BBG0.00	[M]Fibroma NOS
BBG0.11	[M]Fibroma durum
BBG1.00	[M]Fibrosarcoma NOS
BBG2.00	[M]Fibromyxoma
BBG2.11	[M]Myxofibroma NOS
BBG3.00	[M]Fibromyxosarcoma
BBG4.00	[M]Periosteal fibroma
BBG6.00	[M]Fascial fibroma
BBG8.00	[M]Infantile fibrosarcoma
BBG9.00	[M]Elastofibroma
BBGA.00	[M]Aggressive fibromatosis
BBGA.11	[M]Desmoid NOS
BBGA.12	[M]Extra-abdominal desmoid
BBGA.13	[M]Invasive fibroma
BBGB.00	[M]Abdominal fibromatosis

BBGB.11	[M]Abdominal desmoid
BBGC.00	[M]Desmoplastic fibroma
BBGD.00	[M]Fibrous histiocytoma NOS
BBGE.00	[M]Atypical fibrous histiocytoma
BBGF.00	[M]Fibrous histiocytoma, malignant
BBGG.00	[M]Fibroxanthoma NOS
BBGG.11	[M]Xanthofibroma
BBGH.00	[M]Atypical fibroxanthoma
BBGJ.00	[M]Fibroxanthoma, malignant
BBGJ.11	[M]Fibroxanthosarcoma
BBGK.00	[M]Dermatofibroma NOS
BBGK.11	[M]Dermatofibroma lenticulare
BBGK.12	[M]Histiocytoma NOS
BBGK.13	[M]Sclerosing haemangioma
BBGK.14	[M]Subepidermal nodular fibrosis
BBGL.00	[M]Dermatofibroma protuberans
BBGM.00	[M]Dermatofibrosarcoma NOS
BBGN.00	[M]Myofibromatosis
BBGP.00	[M]Pigmented dermatofibrosarcoma protuberans
BBGz.00	[M]Fibromatous neoplasm NOS
BBH..00	[M]Myxomatous neoplasms
BBH0.00	[M]Myxoma NOS
BBH1.00	[M]Myxosarcoma
BBHZ.00	[M]Angiomyxoma
BBHz.00	[M]Myxomatous neoplasm NOS
BBJ..00	[M]Lipomatous neoplasms
BBJ0.00	[M]Lipoma NOS
BBJ1.00	[M]Liposarcoma NOS
BBJ2.00	[M]Fibrolipoma
BBJ2.11	[M]Fibroma molle
BBJ2.12	[M]Soft fibroma
BBJ3.00	[M]Liposarcoma, well differentiated type
BBJ4.00	[M]Fibromyxolipoma
BBJ4.11	[M]Myxolipoma
BBJ5.00	[M]Myxoid liposarcoma
BBJ5.12	[M]Myxoliposarcoma
BBJ7.00	[M]Pleomorphic liposarcoma
BBJ8.00	[M]Mixed type liposarcoma
BBJ9.00	[M]Intramuscular lipoma
BBJ9.11	[M]Infiltrating lipoma
BBJA.00	[M]Spindle cell lipoma
BBJB.00	[M]Angiolipomatous neoplasms
BBJB000	[M]Angiomyolipoma
BBJB200	[M]Angiolipoma NOS
BBJC.00	[M]Myelolipoma
BBJD.00	[M]Hibernoma
BBJD.11	[M]Brown fat tumour
BBJF.00	[M]Pleomorphic lipoma
BBJH.00	[M]Dedifferentiated liposarcoma
BBJz.00	[M]Lipomatous neoplasms NOS
BBK..00	[M]Myomatous neoplasms
BBK0.00	[M]Leiomyomatous neoplasms
BBK0000	[M]Leiomyoma NOS
BBK0011	[M]Fibroid uterus
BBK0012	[M]Fibromyoma
BBK0013	[M]Leiomyofibroma
BBK0014	[M]Myofibroma
BBK0100	[M]Intravascular leiomyomatosis

BBK0200	[M]Leiomyosarcoma NOS
BBK0300	[M]Epithelioid leiomyoma
BBK0311	[M]Leiomyoblastoma
BBK0400	[M]Epithelioid leiomyosarcoma
BBK0500	[M]Cellular leiomyoma
BBK0700	[M]Myxoid leiomyosarcoma
BBK0z00	[M]Leiomyomatous neoplasm NOS
BBK1.00	[M]Angiomyomatous neoplasms
BBK1000	[M]Angiomyoma
BBK1011	[M]Angioleiomyoma
BBK1012	[M]Vascular leiomyoma
BBK1100	[M]Angiomyosarcoma
BBK1z00	[M]Angiomyomatous neoplasm NOS
BBK2.00	[M]Myoma and myosarcoma
BBK2000	[M]Myoma
BBK2100	[M]Myosarcoma
BBK2z00	[M]Myoma or myosarcoma NOS
BBK3.00	[M]Rhabdomyomatous neoplasms
BBK3000	[M]Rhabdomyoma NOS
BBK3100	[M]Rhabdomyosarcoma NOS
BBK3200	[M]Pleomorphic rhabdomyosarcoma
BBK3500	[M]Adult rhabdomyoma
BBK3600	[M]Embryonal rhabdomyosarcoma
BBK3611	[M]Sarcoma botryoides
BBK3700	[M]Alveolar rhabdomyosarcoma
BBK3800	[M]Smooth muscle tumour NOS
BBKz.00	[M]Myomatous neoplasm NOS
BBL..00	[M]Complex mixed and stromal neoplasms
BBL0.00	[M]Endometrial stromal sarcoma
BBL3.00	[M]Pleomorphic adenoma
BBL3.11	[M]Chondroid syringoma
BBL3.12	[M]Mixed tumour NOS
BBL4.00	[M]Mixed tumour, malignant, NOS
BBL5.00	[M]Mullerian mixed tumour
BBL6.00	[M]Mesodermal mixed tumour
BBL7.00	[M]Mixed and stromal renal neoplasms
BBL7.11	[M]Nephromas and nephroblastomas
BBL7000	[M]Mesoblastic nephroma
BBL7100	[M]Nephroblastoma NOS
BBL7111	[M]Adenosarcoma
BBL7112	[M]Wilms' tumour
BBL8.00	[M]Hepatoblastoma
BBL9.00	[M]Carcinosarcoma NOS
BBLA.00	[M]Carcinosarcoma, embryonal type
BBLA.11	[M]Pneumoblastoma
BBLB.00	[M]Myoepithelioma
BBLC.00	[M]Mesenchymomas
BBLCz00	[M]Mesenchymoma NOS
BBLD.00	[M]Embryonal sarcoma
BBLE.00	[M]Adenosarcoma
BBLF.00	[M]Endometrial stromal nodule
BBLG.00	[M]Carcinoma in pleomorphic adenoma
BBLH.00	[M]Rhabdoid sarcoma
BBLJ.00	[M]Clear cell sarcoma of kidney
BBLM.00	[M]Pulmonary blastoma
BBLz.00	[M]Complex mixed or stromal neoplasm NOS
BBM..00	[M]Fibroepithelial neoplasms
BBM0.00	[M]Brenner tumours

BBM0000	[M]Brenner tumour, borderline malignancy
BBM0100	[M]Brenner tumour, malignant
BBM0z00	[M]Brenner tumour NOS
BBM1.00	[M]Fibroadenoma NOS
BBM2.00	[M]Intracanalicular fibroadenoma NOS
BBM3.00	[M]Pericanalicular fibroadenoma
BBM4.00	[M]Adenofibroma NOS
BBM4.11	[M]Cystadenofibroma NOS
BBM5.00	[M]Serous adenofibroma
BBM6.00	[M]Mucinous adenofibroma
BBM7.00	[M]Cellular intracanalicular fibroadenoma
BBM7.12	[M]Fibroadenoma phyllodes
BBM7.13	[M]Giant fibroadenoma NOS
BBM8.00	[M]Cystosarcoma phyllodes NOS
BBM9.00	[M]Cystosarcoma phyllodes, malignant
BBMA.00	[M]Juvenile fibroadenoma
BBMB.00	[M]Giant fibroadenoma
BBMz.00	[M]Fibroepithelial neoplasm NOS
BBN..00	[M]Synovial neoplasms
BBN1.00	[M]Synovial sarcoma NOS
BBN1.11	[M]Synovioma NOS
BBN4.00	[M]Synovial sarcoma, biphasic type
BBN5.00	[M]Clear cell sarcoma of tendons and aponeuroses
BBNz.00	[M]Synovial neoplasm NOS
BBP..00	[M]Mesothelial neoplasms
BBP1.00	[M]Mesothelioma, malignant
BBP5.00	[M]Epithelioid mesothelioma, malignant
BBP8.00	[M]Adenomatoid tumour NOS
BBP9.00	[M]Cystic mesothelioma
BBPX.00	[M]Mesothelioma, unspecified
BBPz.00	[M]Mesothelial neoplasm NOS
BBQ..00	[M]Germ cell neoplasms
BBQ0.00	[M]Dysgerminoma
BBQ1.00	[M]Seminomas
BBQ1000	[M]Seminoma, anaplastic type
BBQ1100	[M]Spermatocytic seminoma
BBQ1z00	[M]Seminoma NOS
BBQ2.00	[M]Germinoma
BBQ3.00	[M]Embryonal carcinoma NOS
BBQ4.00	[M]Endodermal sinus tumour
BBQ4.12	[M]Orchioblastoma
BBQ4.14	[M]Yolk sac tumour
BBQ6.00	[M]Gonadoblastoma
BBQ7.00	[M]Teratomas
BBQ7011	[M]Adult cystic teratoma
BBQ7012	[M]Mature teratoma
BBQ7100	[M]Teratoma NOS
BBQ7200	[M]Teratoma, malignant, NOS
BBQ7211	[M]Embryonal teratoma
BBQ7212	[M]Immature teratoma
BBQ7213	[M]Teratoblastoma, malignant
BBQ7400	[M]Malignant teratoma, undifferentiated type
BBQ7500	[M]Malignant teratoma, intermediate type
BBQ7z00	[M]Teratoma NOS
BBQ8.00	[M]Dermoid cyst
BBQ8.11	[M]Dermoid NOS
BBQ9.00	[M]Dermoid cyst with malignant transformation
BBQA000	[M]Struma ovarii NOS

BBQA100	[M]Struma ovarii, malignant
BBQA200	[M]Strumal carcinoid
BBQB.00	[M]Mixed germ cell tumour
BBQz.00	[M]Germ cell neoplasm NOS
BBR..00	[M]Trophoblastic neoplasms
BBR0.00	[M]Hydatidiform mole NOS
BBR0.11	[M]Hydatid mole
BBR1.00	[M]Invasive hydatidiform mole
BBR1.11	[M]Chorioadenoma
BBR1.13	[M]Invasive mole NOS
BBR2.00	[M]Choriocarcinoma
BBR3.00	[M]Choriocarcinoma combined with teratoma
BBR4.00	[M]Malignant teratoma, trophoblastic
BBR5.00	[M]Partial hydatidiform mole
BBR6.00	[M]Placental site trophoblastic tumour
BBR7.00	[M]Classical hydatidiform mole
BBR8.00	[M]Complete hydatidiform mole
BBRz.00	[M]Trophoblastic neoplasm NOS
BBS..00	[M]Mesonephromas
BBS2.00	[M]Mesonephroma, malignant
BBS3.00	[M]Endosalpingioma
BBT..00	[M]Blood vessel tumours
BBT..11	[M]Haemangiomatous tumours
BBT0.00	[M]Haemangioma NOS
BBT0.11	[M]Angioma NOS
BBT0.12	[M]Chorioangioma
BBT1.00	[M]Haemangiosarcoma
BBT1.11	[M]Angiosarcoma
BBT2.00	[M]Cavernous haemangioma
BBT3.00	[M]Venous haemangioma
BBT4.00	[M]Racemose haemangioma
BBT4.11	[M]Arteriovenous haemangioma
BBT7100	[M]Haemangioendothelioma, malignant
BBT7z11	[M]Angioendothelioma
BBT8.00	[M]Capillary haemangioma
BBT8.12	[M]Infantile haemangioma
BBT8.13	[M]Juvenile haemangioma
BBT8.14	[M]Plexiform haemangioma
BBT9.00	[M]Intramuscular haemangioma
BBTA.00	[M]Kaposi's sarcoma
BBTB.00	[M]Angiokeratoma
BBTC.00	[M]Verrucous keratotic haemangioma
BBTD100	[M]Haemangiopericytoma NOS
BBTE.00	[M]Angiofibroma NOS
BBTE.11	[M]Juvenile angiofibroma
BBTF.00	[M]Haemangioblastoma
BBTF.11	[M]Angioblastoma
BBTG.00	[M]Epithelioid haemangioma
BBTH.00	[M]Histiocytoid haemangioma
BBTJ.00	[M]Epithelioid haemangioendothelioma NOS
BBTK.00	[M]Epithelioid haemangioendothelioma, malignant
BBTL.00	[M]Intravascular bronchial alveolar tumour
BBU..00	[M]Lymphatic vessel tumours
BBU..11	[M]Lymphangiomatous tumours
BBU0.00	[M]Lymphangioma NOS
BBU1.00	[M]Lymphangiosarcoma
BBU2.00	[M]Capillary lymphangioma
BBU3.00	[M]Cavernous lymphangioma

BBU4.00	[M]Cystic lymphangioma
BBU4.11	[M]Cystic hygroma
BBU4.12	[M]Hygroma
BBU5.00	[M]Lymphangiomyoma
BBU6.00	[M]Lymphangiomyomatosis
BBU7.00	[M]Haemolymphangioma
BBV..00	[M]Osteomas and osteosarcomas
BBV..12	[M]Parosteal osteosarcoma
BBV0.00	[M]Osteoma NOS
BBV1.00	[M]Osteosarcoma NOS
BBV1.11	[M]Osteoblastic sarcoma
BBV1.12	[M]Osteochondrosarcoma
BBV1.13	[M]Osteogenic sarcoma NOS
BBV2.00	[M]Chondroblastic osteosarcoma
BBV3.00	[M]Fibroblastic osteosarcoma
BBV4.00	[M]Telangiectatic osteosarcoma
BBV5.00	[M]Osteosarcoma in Paget's disease of bone
BBV7.00	[M]Osteoid osteoma NOS
BBV8.00	[M]Osteoblastoma
BBV8.11	[M]Giant osteoid osteoma
BBV9.00	[M]Myxoid chondrosarcoma
BBVA.00	[M] Small cell osteosarcoma
BBVz.00	[M]Osteoma or osteosarcoma NOS
BBW..00	[M]Chondromatous neoplasms
BBW0.00	[M]Osteochondroma
BBW0.11	[M]Cartilaginous exostosis
BBW0.12	[M]Ecchondroma
BBW0.13	[M]Osteocartilaginous exostosis
BBW1.00	[M]Osteochondromatosis NOS
BBW1.11	[M]Ecchondrosis
BBW2.00	[M]Chondroma NOS
BBW2.11	[M]Enchondroma
BBW3.00	[M]Chondromatosis NOS
BBW4.00	[M]Chondrosarcoma NOS
BBW4.11	[M]Fibrochondrosarcoma
BBW5.11	[M]Periosteal chondroma
BBW6.00	[M]Juxtacortical chondrosarcoma
BBW7.00	[M]Chondroblastoma NOS
BBW7.11	[M]Chondromatous giant cell tumour
BBW9.00	[M]Mesenchymal chondrosarcoma
BBWA.00	[M]Chondromyxoid fibroma
BBWz.00	[M]Chondromatous neoplasm NOS
BBX..00	[M]Giant cell tumours
BBX0.00	[M]Giant cell tumour of bone NOS
BBX0.11	[M]Osteoclastoma
BBX1.11	[M]Giant cell bone sarcoma
BBX1.12	[M]Osteoclastoma, malignant
BBX2.00	[M]Giant cell tumour of soft parts NOS
BBXz.00	[M]Giant cell tumour NOS
BBY..00	[M]Miscellaneous bone tumours
BBY0.00	[M]Ewing's sarcoma
BBY0.11	[M]Endothelial bone sarcoma
BBY1.00	[M]Adamantinoma of long bones
BBY1.11	[M]Tibial adamantinoma
BBY2.00	[M]Ossifying fibroma
BBY2.11	[M]Ossifying fibroma
BBY2.12	[M]Osteofibroma
BBYz.00	[M]Miscellaneous bone tumour NOS

BBZ..00	[M]Odontogenic tumours
BBZ1.00	[M]Odontogenic tumour NOS
BBZ3.00	[M]Dentinoma
BBZ4.00	[M]Cementoma NOS
BBZ6.00	[M]Cementifying fibroma
BBZ7.00	[M]Gigantiform cementoma
BBZ8.00	[M]Odontoma NOS
BBZB.00	[M]Ameloblastic fibro-odontoma
BBZC.00	[M]Ameloblastic odontosarcoma
BBZD.00	[M]Adenomatoid odontogenic tumour
BBZE.00	[M]Calcifying odontogenic cyst
BBZF.00	[M]Ameloblastoma NOS
BBZF.11	[M]Adamantinoma NOS
BBZG.00	[M]Ameloblastoma, malignant
BBZJ.00	[M]Squamous odontogenic tumour
BBZK.00	[M]Odontogenic myxoma
BBZL.00	[M]Odontogenic fibroma NOS
BBZM.00	[M]Ameloblastic fibroma
BBZN.00	[M]Ameloblastic fibrosarcoma
BBZP.00	[M]Calcifying epithelial odontogenic tumour
BBa..00	[M]Miscellaneous tumours
BBa0.00	[M]Craniopharyngioma
BBa1.00	[M]Pinealoma
BBa2.00	[M]Pineocytoma
BBa3.00	[M]Pineoblastoma
BBa4.00	[M]Melanotic neuroectodermal tumour
BBa4.11	[M]Melanoameloblastoma
BBa4.12	[M]Melanotic progonoma
BBa5.00	[M]Chordoma
BBaz.00	[M]Miscellaneous tumour NOS
BBb..00	[M]Gliomas
BBb0.00	[M]Glioma, malignant
BBb0.11	[M]Glioma NOS
BBb0.12	[M]Gliosarcoma
BBb1.00	[M]Gliomatosis cerebri
BBb2.00	[M]Mixed glioma
BBb2.11	[M]Mixed glioma
BBb3.00	[M]Subependymal glioma
BBb3.11	[M]Subependymal astrocytoma NOS
BBb3.12	[M]Subependymal astrocytoma NOS
BBb3.13	[M]Subependymoma
BBb4.00	[M]Subependymal giant cell astrocytoma
BBb5.00	[M]Choroid plexus papilloma NOS
BBb7.00	[M]Ependymoma NOS
BBb8.00	[M]Ependymoma, anaplastic type
BBb8.11	[M]Ependymoblastoma
BBb9.00	[M]Papillary ependymoma
BBbA.00	[M]Myxopapillary ependymoma
BBbB.00	[M]Astrocytoma NOS
BBbB.11	[M]Astrocytic glioma
BBbC.00	[M]Astrocytoma, anaplastic type
BBbE.00	[M]Gemistocytic astrocytoma
BBbF.00	[M]Fibrillary astrocytoma
BBbG.00	[M]Pilocytic astrocytoma
BBbG.11	[M]Juvenile astrocytoma
BBbG.12	[M]Piloid astrocytoma
BBbJ.00	[M]Spongioblastoma polare
BBbK.00	[M]Astroblastoma

BBbL.00	[M]Glioblastoma NOS
BBbL.11	[M]Glioblastoma multiforme
BBbM.00	[M]Giant cell glioblastoma
BBbQ.00	[M]Oligodendroglioma NOS
BBbR.00	[M]Oligodendroglioma, anaplastic type
BBbS.00	[M]Oligodendroblastoma
BBbT.00	[M]Medulloblastoma NOS
BBbU.00	[M]Desmoplastic medulloblastoma
BBbV.00	[M]Medullomyoblastoma
BBbW.00	[M]Cerebellar sarcoma NOS
BBbZ.00	[M]Pleomorphic xanthoastrocytoma
BBba.00	[M]Primitive neuroectodermal tumour
BBbz.00	[M]Glioma NOS
BBc..00	[M]Neuroepitheliomatous neoplasms
BBc0.00	[M]Ganglioneuromatous neoplasms
BBc0000	[M]Ganglioneuroma
BBc0011	[M]Gangliocytoma
BBc0100	[M]Ganglioneuroblastoma
BBc0200	[M]Ganglioneuromatosis
BBc1.00	[M]Neuroblastoma NOS
BBc2.00	[M]Medulloepithelioma NOS
BBc4.00	[M]Neuroepithelioma NOS
BBc6.00	[M]Ganglioglioma
BBc7.00	[M]Neurocytoma
BBc7.11	[M]Neuroastrocytoma
BBc9.00	[M]Retinoblastomas
BBc9z00	[M]Retinoblastoma NOS
BBcA.00	[M]Olfactory neurogenic tumour
BBcC.00	[M]Aesthesioneuroblastoma
BBcC.11	[M]Olfactory neuroblastoma
BBcz.00	[M]Neuroepitheliomatous neoplasm NOS
BBd..00	[M]Meningiomas
BBd0.00	[M]Meningioma NOS
BBd1.12	[M]Multiple meningiomatosis
BBd2.00	[M]Meningioma, malignant
BBd2.11	[M]Leptomeningeal sarcoma
BBd3.00	[M]Meningotheliomatous meningioma
BBd4.00	[M]Fibrous meningioma
BBd5.00	[M]Psammomatous meningioma
BBd6.00	[M]Angiomatous meningioma
BBd7.00	[M]Haemangioblastic meningioma
BBd7.11	[M]Angioblastic meningioma
BBd8.00	[M]Haemangiopericytic meningioma
BBd9.00	[M]Transitional meningioma
BBdz.00	[M]Meningioma NOS
BBe..00	[M]Nerve sheath tumour
BBe..11	[M]Neurofibromas
BBe0.00	[M]Neurofibroma NOS
BBe1.00	[M]Neurofibromatosis NOS
BBe1.11	[M]Multiple neurofibromatosis
BBe1.12	[M]Von Recklinghausen's disease
BBe2.00	[M]Neurofibrosarcoma
BBe3.00	[M]Melanotic neurofibroma
BBe4.00	[M]Plexiform neurofibroma
BBe5.00	[M]Neurilemmoma NOS
BBe5.11	[M]Acoustic neuroma
BBe5.12	[M]Neurinoma
BBe5.13	[M]Schwannoma NOS

BBe6.00	[M]Neurinomatosis
BBe7.00	[M]Neurilemmoma, malignant
BBe7.11	[M]Schwannoma, malignant
BBe8.00	[M]Neuroma NOS
BBe9.00	[M]Triton tumour, malignant
BBeA.00	[M]Neurothekeoma
BBez.00	[M]Nerve sheath tumour NOS
BBf..00	[M]Granular cell tumours and alveolar soft part sarcoma
BBf0.00	[M]Granular cell tumour NOS
BBg..00	[M]Lymphomas, NOS or diffuse
BBg1.00	[M]Malignant lymphoma NOS
BBg1.11	[M]Lymphoma NOS
BBg1000	[M]Malignant lymphoma, diffuse NOS
BBg2.00	[M]Malignant lymphoma, non Hodgkin's type
BBg2.11	[M]Non Hodgkins lymphoma
BBg3.00	[M]Malignant lymphoma, undifferentiated cell type NOS
BBg4.00	[M]Malignant lymphoma, stem cell type
BBg5.00	[M]Malignant lymphoma, convoluted cell type NOS
BBg7.00	[M]Malignant lymphoma, lymphoplasmacytoid type
BBg8.00	[M]Malignant lymphoma, immunoblastic type
BBgA.00	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
BBgB.00	[M]Malignant lymphoma, follicular centre cell NOS
BBgC.00	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
BBgC.11	[M]Lymphocytic lymphoma NOS
BBgC.12	[M]Lymphocytic lymphosarcoma NOS
BBgD.00	[M]Malig lymphoma, lymphocytic, intermediate different NOS
BBgE.00	[M]Malignant lymphoma, centrocytic
BBgG.00	[M]Malignant lymphoma, lymphocytic, poorly different NOS
BBgG.11	[M]Lymphoblastic lymphosarcoma NOS
BBgG.12	[M]Lymphoblastic lymphoma NOS
BBgG.13	[M]Lymphoblastoma NOS
BBgJ.00	[M]Malignant lymphoma, centroblastic type NOS
BBgK.00	[M]Malig lymphoma, follicular centre cell, non-cleaved NOS
BBgL.00	[M]Malignant lymphoma, small lymphocytic NOS
BBgM.00	[M]Malignant lymphoma, small cleaved cell, diffuse
BBgN.00	[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse
BBgP.00	[M]Malignant lymphoma, mixed small and large cell, diffuse
BBgQ.00	[M]Malignant lymphomatous polyposis
BBgR.00	[M]Malignant lymphoma, large cell, diffuse NOS
BBgS.00	[M]Malignant lymphoma, large cell, cleaved, diffuse
BBgT.00	[M]Malignant lymphoma, large cell, noncleaved, diffuse
BBgV.00	[M]Malignant lymphoma, small cell, noncleaved, diffuse
BBgz.00	[M]Lymphoma, diffuse or NOS
BBh0.11	[M]Reticulum cell sarcoma NOS
BBj..00	[M]Hodgkin's disease
BBj0.00	[M]Hodgkin's disease NOS
BBj1.00	[M]Hodgkin's disease, lymphocytic predominance
BBj1000	[M]Hodgkin,s disease, lymphocytic predominance, diffuse
BBj1100	[M]Hodgkin,s disease, lymphocytic predominance, nodular
BBj2.00	[M]Hodgkin's disease, mixed cellularity
BBj6.00	[M]Hodgkin's disease, nodular sclerosis NOS
BBj6000	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic predom
BBj6100	[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity
BBj6200	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic deplet
BBj7.00	[M]Hodgkin's disease, nodular sclerosis, cellular phase
BBjA.00	[M]Hodgkin's sarcoma
BBjz.00	[M]Hodgkin's disease NOS
BBk..00	[M]Lymphomas, nodular or follicular

BBk0.00	[M]Malignant lymphoma, nodular NOS
BBk0.11	[M]Brill - Symmers' disease
BBk0.12	[M]Follicular lymphosarcoma NOS
BBk0.13	[M]Giant follicular lymphoma
BBk5.00	[M]Malig lymp, follicular centre cell, cleaved, follicular
BBk7.00	[M]Malignant lymphoma, centroblastic type, follicular
BBkz.00	[M]Lymphoma, nodular or follicular NOS
BBl..00	[M]Mycosis fungoides
BBl0.00	[M]Mycosis fungoides
BBlz.00	[M]Mycosis fungoides NOS
BBm..00	[M]Miscellaneous reticuloendothelial neoplasms
BBm1.00	[M]Malignant histiocytosis
BBm1.11	[M]Malignant reticulosis
BBm3.00	[M]Letterer - Siwe disease
BBm3.12	[M]Acute progressive histiocytosis X
BBm4.00	[M]True histiocytic lymphoma
BBm5.00	[M] Peripheral T-cell lymphoma NOS
BBm6.00	[M] Alpha heavy chain disease
BBm7.00	[M] Monoclonal gammopathy
BBm8.00	[M] Angioimmunoblastic lymphadenopathy
BBm9.00	[M] Monocytoid B-cell lymphoma
BBmC.00	[M] T-gamma lymphoproliferative disease
BBmD.00	[M] Cutaneous lymphoma
BBmH.00	[M] Large cell lymphoma
BBmK.00	[M]Waldenstrom's macroglobulinaemia
BBmz.00	[M]Miscellaneous reticuloendothelial neoplasm NOS
BBn..00	[M]Plasma cell tumours
BBn0.00	[M]Plasma cell myeloma
BBn0.11	[M]Multiple myeloma
BBn0.12	[M]Myeloma NOS
BBn0.13	[M]Myelomatosis
BBn0.14	[M]Plasmacytic myeloma
BBn2.00	[M]Plasmacytoma NOS
BBn2.11	[M]Monostotic myeloma
BBnz.00	[M]Plasma cell tumour NOS
BBp..00	[M]Mast cell tumours
BBp0.00	[M]Mastocytoma NOS
BBp2.00	[M]Malignant mastocytosis
BBr..00	[M]Leukaemias
BBr0.00	[M]Leukaemias unspecified
BBr0000	[M]Leukaemia NOS
BBr0100	[M]Acute leukaemia NOS
BBr0111	[M]Blast cell leukaemia
BBr0113	[M]Stem cell leukaemia
BBr0300	[M]Chronic leukaemia NOS
BBr0z00	[M]Leukaemia unspecified, NOS
BBr2.00	[M]Lymphoid leukaemias
BBr2000	[M]Lymphoid leukaemia NOS
BBr2011	[M]Lymphatic leukaemia
BBr2100	[M]Acute lymphoid leukaemia
BBr2300	[M]Chronic lymphoid leukaemia
BBr2500	[M]Prolymphocytic leukaemia
BBr2600	[M]Burkitt's cell leukaemia
BBr2700	[M]Adult T-cell leukaemia/lymphoma
BBr2z00	[M]Other lymphoid leukaemia NOS
BBr3.00	[M]Plasma cell leukaemias
BBr4.00	[M]Erythroleukaemias
BBr6.00	[M]Myeloid leukaemias

BBr6000	[M]Myeloid leukaemia NOS
BBr6011	[M]Granulocytic leukaemia NOS
BBr6012	[M]Myelosis NOS
BBr6100	[M]Acute myeloid leukaemia
BBr6300	[M]Chronic myeloid leukaemia
BBr6600	[M]Acute promyelocytic leukaemia
BBr6700	[M]Acute myelomonocytic leukaemia
BBr6800	[M]Chronic myelomonocytic leukaemia
BBr6z00	[M]Other myeloid leukaemia NOS
BBr8.00	[M]Eosinophilic leukaemias
BBr8000	[M]Eosinophilic leukaemia
BBrA111	[M]Thrombocytic leukaemia
BBrA400	[M]Hairy cell leukaemia
BBrA500	[M]Acute megakaryoblastic leukaemia
BBrA700	[M]Acute myelofibrosis
BBrz.00	[M]Leukaemia NOS
BBs..00	[M]Misc myeloproliferative and lymphoproliferative disorders
BBs0.00	[M]Polycythaemia vera
BBs0.11	[M]Polycythaemia rubra vera
BBs1.00	[M]Acute panmyelosis
BBs2.00	[M]Chronic myeloproliferative disease
BBs3.00	[M]Myelosclerosis with myeloid metaplasia
BBs4.00	[M]Idiopathic thrombocythaemia
BBs5.00	[M]Chronic lymphoproliferative disease
BBsz.00	[M]Misc myeloproliferative or lymphoproliferative dis NOS
BBv..00	[M]Myelodysplastic syndrome
BBv0.00	[M]Monocytoid B-cell lymphoma
BBv2.00	[M]AngiocentricT-cell lymphoma
BBy..00	[M]No microscopic confirmation of tumour
BBz..00	[M]Neoplasm morphology NOS
By...00	Neoplasms otherwise specified
Byu..00	[X]Additional neoplasm classification terms
Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
Byu1.00	[X]Malignant neoplasm of digestive organs
Byu1100	[X]Other specified carcinomas of liver
Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
Byu1300	[X]Malignant neoplsm/ill-defin sites within digestive system
Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga
Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
Byu2100	[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura
Byu2400	[X]Malignant neoplasm/ill-defined sites within resp system
Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
Byu3200	[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage
Byu3300	[X]Malignant neoplasm/bone+articular cartilage, unspecified
Byu4.00	[X]Melanoma and other malignant neoplasms of skin
Byu4000	[X]Malignant melanoma of other+unspecified parts of face
Byu4100	[X]Malignant melanoma of skin, unspecified
Byu4200	[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face
Byu4300	[X]Malignant neoplasm of skin, unspecified
Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
Byu5000	[X]Mesothelioma of other sites
Byu5011	[X]Mesothelioma of lung
Byu5100	[X]Mesothelioma, unspecified
Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified
Byu5A00	[X]Malignant neoplasm overlapping lesion of skin
Byu6.00	[X]Malignant neoplasm of breast
Byu7.00	[X]Malignant neoplasm of female genital organs
Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified

Byu7100	[X]Malignant neoplasm/other specified female genital organs
Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
Byu8.00	[X]Malignant neoplasm of male genital organs
Byu8000	[X]Malignant neoplasm/other specified male genital organs
Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
Byu9.00	[X]Malignant neoplasm of urinary tract
ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
ByuA200	[X]Malignant neoplasm of meninges, unspecified
ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
ByuC000	[X]Malignant neoplasm of other specified sites
ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
ByuC700	[X]Secondary malignant neoplasm of other specified sites
ByuC800	[X]Malignant neoplasm without specification of site
ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
ByuD000	[X]Other Hodgkin's disease
ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
ByuD500	[X]Other lymphoid leukaemia
ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
ByuDD00	[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas
ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
ByuDF11	[X]Non-Hodgkin's lymphoma NOS
ByuE.00	[X]Malignant neoplasms/independent (primary) multiple sites
ByuE000	[X]Malignant neoplasms/independent(primary)multiple sites
ByuF000	[X]Carcinoma in situ/other+unspecified parts of intestine
ByuF100	[X]Carcinoma in situ of other specified digestive organs
ByuF900	[X]Carcinoma in situ of skin, unspecified
ByuFC00	[X]Carcinoma in situ of oth+unspecified male genital organs
ByuFF00	[X]Melanoma in situ, unspecified
ByuFG00	[X]Other carcinoma in situ of breast
ByuH.00	[X]Neoplasms of uncertain and unknown behaviour
ByuHD00	[X]Myelodysplastic syndrome, unspecified
Bz...00	Neoplasms NOS

Appendix 6-1k: Read codes used to identify people with gastrointestinal complications

Read codes	Git Read code descriptions
J520000	Acute constipation
198..11	C/O - nausea
199..11	C/O - vomiting
J520400	Chronic constipation
J520100	Chronic constipation with overflow
J520200	Chronic constipation without overflow
19C..00	Constipation
19CZ.00	Constipation NOS
J520z00	Constipation NOS
19C..11	Constipation symptom

1943.00	Difficulty swallowing liquids
1942.00	Difficulty swallowing solids
J520300	Drug induced constipation
194..11	Dysphagia
198..00	Nausea
198Z.00	Nausea NOS
1982.00	Nausea present
198..12	Nausea symptoms
J520y00	Other specified constipation
J162.00	Persistent vomiting
J162z00	Persistent vomiting NOS
1992.00	Vomiting
199..00	Vomiting
1996.00	Vomiting - bile stained
199Z.00	Vomiting NOS
199..14	Vomiting symptoms
R070300	[D]Drug induced vomiting
R072.00	[D]Dysphagia
R072z00	[D]Dysphagia NOS
R070000	[D]Nausea
R070.00	[D]Nausea and vomiting
R070z00	[D]Nausea and vomiting NOS
R070100	[D]Vomiting
medcode	gitdescription
J520000	Acute constipation
198..11	C/O - nausea
199..11	C/O - vomiting
J520400	Chronic constipation
J520100	Chronic constipation with overflow
J520200	Chronic constipation without overflow
19C..00	Constipation
19CZ.00	Constipation NOS
J520z00	Constipation NOS
19C..11	Constipation symptom
1943.00	Difficulty swallowing liquids
1942.00	Difficulty swallowing solids
J520300	Drug induced constipation
194..11	Dysphagia
198..00	Nausea
198Z.00	Nausea NOS
1982.00	Nausea present
198..12	Nausea symptoms
J520y00	Other specified constipation
J162.00	Persistent vomiting
J162z00	Persistent vomiting NOS
1992.00	Vomiting
199..00	Vomiting
1996.00	Vomiting - bile stained
199Z.00	Vomiting NOS
199..14	Vomiting symptoms
R070300	[D]Drug induced vomiting
R072.00	[D]Dysphagia
R072z00	[D]Dysphagia NOS
R070000	[D]Nausea
R070.00	[D]Nausea and vomiting
R070z00	[D]Nausea and vomiting NOS
R070100	[D]Vomiting

Appendix 6-1l: Read codes used to identify people with infections

Read codes	Infection Read code descriptions
H530300	Abscess of lung with pneumonia
A396.11	Actinomycotic sepsis
A395.00	Actinomycotic septicaemia
F011z11	Acute aseptic meningitis
H023.00	Acute bacterial pharyngitis
H023z00	Acute bacterial pharyngitis NOS
N300.12	Acute bone infection
H060A00	Acute bronchitis due to mycoplasma pneumoniae
H020.00	Acute gangrenous pharyngitis
A702000	Acute hep B with delta-agent (coinfection) with hep coma
F501200	Acute infection of pinna
H050.00	Acute laryngopharyngitis
H00..00	Acute nasopharyngitis
A4zy100	Acute necrotising encephalitis
H02..00	Acute pharyngitis
H02z.00	Acute pharyngitis NOS
H021.00	Acute phlegmonous pharyngitis
H023000	Acute pneumococcal pharyngitis
H0z..00	Acute respiratory infection NOS
H0...00	Acute respiratory infections
A918000	Acute secondary syphilitic meningitis
H023100	Acute staphylococcal pharyngitis
H022.00	Acute ulcerative pharyngitis
H024.00	Acute viral pharyngitis
A4zy500	Adenoviral encephalitis
A4z1.00	Adenoviral meningitis
A3By000	Aerobacter aerogenes infection
A05y.00	Amoebic infection of other sites
A052.00	Amoebic nondysenteric colitis
A42z.11	Aseptic meningitis
H470.11	Aspiration pneumonia
H470312	Aspiration pneumonia due to vomit
1789.00	Asthma trigger - respiratory infection
H28..00	Atypical pneumonia
A3B..00	Bacterial infections - causative organisms
F00..00	Bacterial meningitis
F00z.00	Bacterial meningitis NOS
F03X.00	Bacterial meningoencephalitis+meningomyelitis,NEC
H22z.00	Bacterial pneumonia NOS
H261.00	Basal pneumonia due to unspecified organism
AC32.11	Beef tapeworm infection
F024.00	Benign recurrent meningitis
J666.00	Biliary sepsis
N302.11	Bone infection
N30zz00	Bone infection NOS
N30z.00	Bone infection NOS
N30z700	Bone infection NOS, of ankle and foot
N30z900	Bone infection NOS, of multiple sites
N30z800	Bone infection NOS, of other specified site
N30z300	Bone infection NOS, of the forearm
N30z400	Bone infection NOS, of the hand
N30z600	Bone infection NOS, of the lower leg
N30z500	Bone infection NOS, of the pelvic/thigh
N30z100	Bone infection NOS, of the shoulder region

N30z200	Bone infection NOS, of the upper arm
N30z000	Bone infection NOS, of unspecified site
H564.00	Bronchiolitis obliterans organising pneumonia
H25..00	Bronchopneumonia due to unspecified organism
SP07Q11	CAUTI - catheter-associated urinary tract infection
A799.11	CMV - Cytomegalovirus infection
A074312	Campylobacter enteritis
AB2y200	Candidal meningitis
AB2y500	Candidal sepsis
AB2y300	Candidal septicaemia
AC10.11	Cat liver fluke infection
SP07Q00	Catheter-associated urinary tract infection
A632.00	Central European encephalitis
AC3z.00	Cestode infection NOS
H06z011	Chest infection
H270.11	Chest infection - influenza with pneumonia
H22..11	Chest infection - other bacterial pneumonia
H21..11	Chest infection - pneumococcal pneumonia
H23..11	Chest infection - pneumonia organism OS
H30..11	Chest infection - unspecified bronchitis
H25..11	Chest infection - unspecified bronchopneumonia
H20..11	Chest infection - viral pneumonia
H06z000	Chest infection NOS
H24..11	Chest infection with infectious disease EC
A78A.00	Chlamydial infection
A78A200	Chlamydial infection of anus and rectum
A78A500	Chlamydial infection of genital organs NEC
A78A100	Chlamydial infection of pharynx
A78AW00	Chlamydial infection, unspecified
H233.00	Chlamydial pneumonia
F022.00	Chronic meningitis
H122.00	Chronic nasopharyngitis
H121.00	Chronic pharyngitis
H121z00	Chronic pharyngitis NOS
H12..00	Chronic pharyngitis and nasopharyngitis
H12z.00	Chronic pharyngitis and nasopharyngitis NOS
K190400	Chronic urinary tract infection
A3Ay200	Clostridium difficile infection
A3A0011	Clostridium histolyticum infection
A3A0.11	Clostridium infection
A3A0111	Clostridium oedematiens infection
A3A0211	Clostridium perfringens infection
A3A0311	Clostridium septicum infection
A3A0411	Clostridium sordellii infection
A3By600	Coccal infection NEC
AB32.00	Coccidioidal meningitis
J437.00	Colitis
A061.11	Colitis - giardial
A081000	Colitis - presumed infectious origin
A081z00	Colitis, enteritis and gastroenteritis presumed infect NOS
A081.00	Colitis, enteritis and gastroenteritis presumed infectious
A081.11	Colitis,enteritis ? infectious
H2B..00	Community acquired pneumonia
A795.00	Coronavirus infection
A420.00	Coxsackie viral meningitis
AB65200	Cryptococcal meningitis
H564.11	Cryptogenic organising pneumonia
A311.00	Cutaneous mycobacterial infections

A311.13	Cutaneous mycobacterial infections
F030711	Cytomegaloviral encephalitis
A799.00	Cytomegalovirus infection
J024.11	Dental infection
AC34.00	Diphyllobothrium infection
AC3y.11	Dog tapeworm infection
AC36.11	Dwarf tapeworm infection
A3B4.11	E.coli infection
H22y011	E.coli pneumonia
A384211	E.coli septicaemia
A421.00	ECHO viral meningitis
AC23000	Echinococcus granulosus infection of bone
F03z.00	Encephalitis NOS
F030900	Encephalitis due to herpes zoster
F032000	Encephalitis due to malaria
F033000	Encephalitis due to meningococcus
F033.00	Encephalitis due to other infection
F030200	Encephalitis due to poliomyelitis
F032.00	Encephalitis due to protozoa
F032z00	Encephalitis due to protozoa NOS
F031.00	Encephalitis due to rickettsia
F030100	Encephalitis due to subacute sclerosing panencephalitis
F033200	Encephalitis due to syphilis unspecified
F033400	Encephalitis due to toxoplasmosis
F032100	Encephalitis due to trypanosomiasis
F033300	Encephalitis due to tuberculosis
F035011	Encephalitis due to varicella
F035000	Encephalitis following chickenpox
F030.00	Encephalitis in viral disease EC
F030z00	Encephalitis in viral disease NOS
F03..00	Encephalitis, myelitis and encephalomyelitis
A081100	Enteritis - presumed infectious origin
A074400	Enteritis due to Yersinia enterocolitica
A076000	Enteritis due to adenovirus
A076100	Enteritis due to enterovirus
A076300	Enteritis due to norovirus
A076200	Enteritis due to rotavirus
A076.00	Enteritis due to specified virus
A076z00	Enteritis due to specified virus NOS
J43..12	Enterocolitis
A070300	Enterohaemorrhagic Escherichia coli infection
A070200	Enteroinvasive Escherichia coli infection
A070000	Enteropathogenic Escherichia coli infection
A070100	Enterotoxigenic Escherichia coli infection
A4y0.00	Enteroviral encephalitis
A79X.00	Enterovirus infection, unspecified
F021.00	Eosinophilic meningitis
A4zy200	Epidemic encephalitis
A271000	Erysipelothrix infection
A271.00	Erysipelothrix infection, unspecified
A271311	Erysipelothrix sepsis
A271100	Erysipelothrix septicaemia
A3B4.00	Escherichia coli infection
F00y212	Escherichia coli meningitis
A384200	Escherichia coli septicaemia
F400500	Eye infection
F4C0.11	Eye infection
AC5..00	Filarial infection and dracontiasis

F4Cy000	Filarial infection of conjunctiva
H530200	Gangrenous pneumonia
J43..11	Gastroenteritis
A081200	Gastroenteritis - presumed infectious origin
J6A..00	Gastroenteritis and colitis of unknown origin
A98y100	Gonococcal meningitis
A98yz12	Gonococcal septicaemia
A384000	Gram negative septicaemia NOS
A3B0100	Group A streptococcus infection
A3B0000	Group B streptococcus infection
A789300	HIV disease resulting in Pneumocystis carinii pneumonia
A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
A789400	HIV disease resulting in multiple infections
A789000	HIV disease resulting in mycobacterial infection
A3B5.00	Haemophilus influenzae infection
A384100	Haemophilus influenzae septicaemia
F000.00	Haemophilus meningitis
2J23.00	Hepatitis A - current infection
J632.00	Hepatitis in other infectious diseases EC
F030411	Herpes simplex encephalitis
A54x100	Herpes simplex meningitis
F011311	Herpes simplex meningitis
A54x400	Herpes simplex pneumonia
A545.00	Herpes simplex septicaemia
A54..11	Herpes simplex viral infection
F030911	Herpes zoster encephalitis
F011211	Herpes zoster meningitis
A530.00	Herpes zoster with meningitis
A541300	Herpetic infection of penis
A543.00	Herpetic meningoencephalitis
AB40.00	Histoplasma capsulatum infection
AB40100	Histoplasma capsulatum with meningitis
AB40500	Histoplasma capsulatum with pneumonia
AB41.00	Histoplasma duboisii infection
AB41100	Histoplasma duboisii with meningitis
AB41500	Histoplasma duboisii with pneumonia
AB4z100	Histoplasmosis with meningitis
AB4z500	Histoplasmosis with pneumonia
H2C..00	Hospital acquired pneumonia
A79B.00	Human papilloma virus infection
H540100	Hypostatic bronchopneumonia
H540000	Hypostatic pneumonia
J41..00	Idiopathic proctocolitis
J41z.00	Idiopathic proctocolitis NOS
J4z6.00	Indeterminate colitis
A07y100	Infantile viral gastroenteritis
SP33000	Infection after infusion
SP33100	Infection after injection
SP33200	Infection after transfusion
SP06800	Infection and inflamm reac due inter ortho device
SP06.00	Infection and inflammation due to internal prosthetic device
A3BC.00	Infection due to ESBL producing bacteria
ADy0200	Infection due to antimicrobial resistant bacteria
A3BD.00	Infection due to carbapenemase producing Enterobacteriacea
A3BE.00	Infection due to enterococcus
SP06.12	Infection due to internal prosthetic device,implant or graft
ADy0.00	Infection due to resistant organism
F52z.11	Infection ear

J083z11	Infection mouth
SP06600	Infection of bone allograft
SP06500	Infection of bone graft
N302U00	Infection of calcaneum
N302A00	Infection of cervical spine
N302F00	Infection of clavicle
N302E00	Infection of coccyx
N302Q00	Infection of femur
N302T00	Infection of fibula
N302H00	Infection of humerus
SP06700	Infection of internal Kirschner wire fixator
N302C00	Infection of lumbar spine
N302M00	Infection of metacarpal
N302X00	Infection of metatarsal
N302P00	Infection of pelvis
N302J00	Infection of radius
N302D00	Infection of sacrum
N302B00	Infection of thoracic spine
K10..00	Infections of kidney
A... 00	Infectious and parasitic diseases
Az...00	Infectious and parasitic diseases NOS
A080100	Infectious colitis
A080.00	Infectious colitis, enteritis and gastroenteritis
A080z00	Infectious colitis, enteritis and gastroenteritis NOS
A082.00	Infectious diarrhoea
A082z00	Infectious diarrhoea NOS
M102.00	Infectious eczematoid dermatitis
A080200	Infectious enteritis
A080300	Infectious gastroenteritis
Q404000	Infectious granuloma
A724.11	Infectious parotitis
H270000	Influenza with bronchopneumonia
H271100	Influenza with pharyngitis
H270.00	Influenza with pneumonia
H270z00	Influenza with pneumonia NOS
H270100	Influenza with pneumonia, influenza virus identified
H56y100	Interstitial pneumonia
F00y411	Klebsiella meningitis
A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters
AA0y000	Leptospiral meningitis
A270000	Listeria infection
A270100	Listeria septicaemia
A270611	Listerial sepsis
H21..00	Lobar (pneumococcal) pneumonia
H260.00	Lobar pneumonia due to unspecified organism
A022000	Local salmonella infection unspecified
A022.00	Localised salmonella infection
H06z100	Lower resp tract infection
SP25800	MRSA infection of postoperative wound
F032011	Malarial encephalitis
F005.00	Meningitis - meningococcal
F004.00	Meningitis - tuberculous
F011z00	Meningitis - viral NOS
F007700	Meningitis due to actinomycosis
F00y000	Meningitis due to aerobacter aerogenes
F010000	Meningitis due to cryptococcus
F00y211	Meningitis due to escherichia coli
F00y200	Meningitis due to escherichia coli

F010.00	Meningitis due to fungal organisms
F007000	Meningitis due to gonococcus
F01y000	Meningitis due to leptospira
F007100	Meningitis due to listeriosis
F007200	Meningitis due to neurosyphilis
F01z.00	Meningitis due to organism NOS
F01..00	Meningitis due to other organisms
F007800	Meningitis due to pertussis
F00y500	Meningitis due to proteus morganii
F00y600	Meningitis due to pseudomonas
F007300	Meningitis due to salmonella
F013.00	Meningitis due to sarcoidosis
F007500	Meningitis due to secondary syphilis
F012.00	Meningitis due to trypanosomiasis
F007600	Meningitis due to typhoid fever
F011.00	Meningitis due to viral organisms EC
F007.00	Meningitis in other bacterial disease classified elsewhere
F02..00	Meningitis of unspecified cause
F033011	Meningococcal encephalitis
A361.00	Meningococcal encephalitis
A36..00	Meningococcal infection
A36z.00	Meningococcal infection NOS
A360.00	Meningococcal meningitis
A365.00	Meningococcal meningitis with acute meningococcal septicaem
A366.00	Meningococcal meningitis with meningococcal septicaemia
A362.00	Meningococcal septicaemia
J41..11	Mucous colitis and/or proctitis
A722.00	Mumps encephalitis
F030511	Mumps encephalitis
F011411	Mumps meningitis
A721.00	Mumps meningitis
A311.12	Mycobacterium marinum infection
A3By300	Mycoplasma infection
A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
AD62.11	Naegleria meningoencephalitis
H1y1z14	Nasal infection
F020.00	Nonpyogenic meningitis
A532300	Ophthalmic herpes zoster infection
A730.00	Ornithosis with pneumonia
F501900	Other acute external ear infections
H05..00	Other acute upper respiratory infections
AD6..00	Other and unspecified infectious and parasitic diseases
SP13100	Other aspiration pneumonia as a complication of care
H22..00	Other bacterial pneumonia
F03y.00	Other causes of encephalitis
AC3..00	Other cestode infection
AC1..11	Other fluke infections
F010z00	Other fungal meningitis
A384z00	Other gram negative septicaemia NOS
J41y.00	Other idiopathic proctocolitis
J41yz00	Other idiopathic proctocolitis NOS
AD...00	Other infectious and parasitic diseases
ADz..00	Other infectious or parasitic disease NOS
A022z00	Other local salmonella infection
F01y.00	Other non-bacterial meningitis
F01yz00	Other non-bacterial meningitis NOS
A02..00	Other salmonella infections
A79y.00	Other specific viral infection

H0y..00	Other specified acute respiratory infections
A3By.00	Other specified bacterial infection
F00y.00	Other specified bacterial meningitis
F00yz00	Other specified bacterial meningitis NOS
AC3y.00	Other specified cestode infection
AD6y.00	Other specified infectious and parasitic disease
Ay...00	Other specified infectious or parasitic diseases
ADy..00	Other specified infectious or parasitic diseases
AA0y.00	Other specified leptospiral infection
A36y.00	Other specified meningococcal infection
A36yz00	Other specified meningococcal infection NOS
H2y..00	Other specified pneumonia or influenza
A02y.00	Other specified salmonella infection
A3Cy.00	Other specified sepsis
A38y.00	Other specified septicaemias
A03y.00	Other specified shigella infection
AA4y.00	Other specified spirochaetal infection
AAy..00	Other specified spirochaetal infections
AC1y.00	Other specified trematode infection
AC1yz00	Other specified trematode infection NOS
A42y.00	Other specified viral meningitis
AA4..00	Other spirochaetal infections
A3C0y00	Other streptococcal sepsis
AC3..11	Other tapeworm infection
A63y.00	Other tick-borne viral encephalitis
A63yz00	Other tick-borne viral encephalitis NOS
AC1..00	Other trematode infections
H05y.00	Other upper respiratory infections of multiple sites
F011y00	Other viral meningitis
A3B1200	Panton-Valentine leucocidin associat staph aureus infection
A797.00	Papovavirus infection
F4C1500	Parasitic conjunctivitis
F401200	Parasitic endophthalmitis NOS
F4D6.00	Parasitic eyelid infestation
F4G1300	Parasitic infestation of orbit
A796.00	Parvovirus infection
AD2..00	Pediculosis and phthirus infections
J574G00	Perianal infection
J57yE00	Pericolitis
J550.00	Peritonitis in infectious diseases EC
A206.00	Plague meningitis
A3By400	Pleuropneumonia-like organism (PPLO) infection
A3B2.00	Pneumococcal infection
F001.00	Pneumococcal meningitis
A382.00	Pneumococcal septicaemia
H22y200	Pneumonia - Legionella
AB24.11	Pneumonia - candidal
H2...00	Pneumonia and influenza
H22y300	Pneumonia due to Gram neg bact
H200.00	Pneumonia due to adenovirus
H22yz00	Pneumonia due to bacteria NOS
H22y000	Pneumonia due to escherichia coli
H222.00	Pneumonia due to haemophilus influenzae
H222.11	Pneumonia due to haemophilus influenzae
H203.00	Pneumonia due to human metapneumovirus
H220.00	Pneumonia due to klebsiella pneumoniae
H231.00	Pneumonia due to mycoplasma pneumoniae
H22yX00	Pneumonia due to other aerobic gram-negative bacteria

H22y.00	Pneumonia due to other specified bacteria
H23..00	Pneumonia due to other specified organisms
H202.00	Pneumonia due to parainfluenza virus
H232.00	Pneumonia due to pleuropneumonia like organisms
H22y100	Pneumonia due to proteus
H221.00	Pneumonia due to pseudomonas
H201.00	Pneumonia due to respiratory syncytial virus
H23z.00	Pneumonia due to specified organism NOS
H224.00	Pneumonia due to staphylococcus
H223.00	Pneumonia due to streptococcus
H223000	Pneumonia due to streptococcus, group B
H26..00	Pneumonia due to unspecified organism
H2z..00	Pneumonia or influenza NOS
H24y300	Pneumonia with Q-fever
H24y000	Pneumonia with actinomycosis
H245.00	Pneumonia with anthrax
H246.00	Pneumonia with aspergillosis
H247000	Pneumonia with candidiasis
H247100	Pneumonia with coccidioidomycosis
H247200	Pneumonia with histoplasmosis
H24..00	Pneumonia with infectious diseases EC
H24z.00	Pneumonia with infectious diseases EC NOS
H24y100	Pneumonia with nocardiasis
H24y.00	Pneumonia with other infectious diseases EC
H24yz00	Pneumonia with other infectious diseases EC NOS
H24y200	Pneumonia with pneumocystis carinii
H24y400	Pneumonia with salmonellosis
H24y500	Pneumonia with toxoplasmosis
H244.00	Pneumonia with tularaemia
H24y600	Pneumonia with typhoid fever
H24y700	Pneumonia with varicella
F030211	Poliomyelitis encephalitis
AC30.11	Pork tapeworm infection
SP13200	Post operative chest infection
K190200	Post operative urinary tract infection
E2A3.11	Post-encephalitis syndrome
F035.00	Postinfectious encephalitis
F035z00	Postinfectious encephalitis NOS
SP25.00	Postoperative infection
SP25z00	Postoperative infection NOS
SP25500	Postoperative wound infection, unspecified
SP25600	Postoperative wound infection-deep
SP25700	Postoperative wound infection-superficial
A520.00	Postvaricella encephalitis
A63y100	Powassan encephalitis
A10..00	Primary tuberculous infection
A10z.00	Primary tuberculous infection NOS
A3B6.00	Proteus infection
A3B6000	Proteus mirabilis infection
A3B6100	Proteus morganii infection
F00y511	Proteus morganii meningitis
J434.00	Pseudomembranous colitis
J431311	Pseudomembranous colitis
J521.12	Pseudomembranous colitis
A3B7.00	Pseudomonas infection
F00y611	Pseudomonas meningitis
A384300	Pseudomonas septicaemia
A310.00	Pulmonary mycobacterial infection

A310000	Pulmonary mycobacterium avium-intracellulare infection
N22yC00	Pyogenic infection of tendon sheath
AC36.12	Rat tapeworm infection
H06z200	Recurrent chest infection
K190300	Recurrent urinary tract infection
K190.11	Recurrent urinary tract infection
1AG..00	Recurrent urinary tract infections
K0B0.00	Ren tubulo-interstital disord infect and parasitic dis EC
K10..11	Renal infections
H5yy.11	Respiratory infection NOS
A798.00	Retrovirus infection
A020.00	Salmonella gastroenteritis
A022100	Salmonella meningitis
A022200	Salmonella pneumonia
A023.00	Salmonella sepsis
A021.00	Salmonella septicaemia
M073.00	Scalp infection
A38z.11	Sepsis
A3C..00	Sepsis
A3Cz.00	Sepsis NOS
A396.00	Sepsis due to Actinomyces
A224.00	Sepsis due to Bacillus anthracis
AB2y511	Sepsis due to Candida
A271300	Sepsis due to Erysipelothrix
A3C3.00	Sepsis due to Gram negative bacteria
A3C3.11	Sepsis due to Gram negative organisms
A3C3000	Sepsis due to Haemophilus influenzae
A270600	Sepsis due to Listeria monocytogenes
A3C1.00	Sepsis due to Staphylococcus
A3C1000	Sepsis due to Staphylococcus aureus
A3C0.00	Sepsis due to Streptococcus
A3C0000	Sepsis due to Streptococcus group A
A3C0100	Sepsis due to Streptococcus group B
A3C0200	Sepsis due to Streptococcus group D
A3C0300	Sepsis due to Streptococcus pneumoniae
A3C2.11	Sepsis due to anaerobes
A3C2.00	Sepsis due to anaerobic bacteria
A3C3y00	Sepsis due to other Gram negative organisms
A3C1y00	Sepsis due to other specified staphylococcus
A3C1z00	Sepsis due to staphylococcus NOS
A38..00	Septicaemia
A38z.00	Septicaemia NOS
A381000	Septicaemia due to Staphylococcus aureus
A383.00	Septicaemia due to anaerobes
A381100	Septicaemia due to coagulase-negative staphylococcus
A380400	Septicaemia due to enterococcus
A384.00	Septicaemia due to other gram negative organisms
A380300	Septicaemia due to streptococcus pneumoniae
A380000	Septicaemia due to streptococcus, group A
A380100	Septicaemia due to streptococcus, group B
A380200	Septicaemia due to streptococcus, group D
A3By500	Serratia infection
A384400	Serratia septicaemia
A9...13	Sexually transmitted infectious diseases
AC13.12	Sheep liver fluke infection
H121000	Simple chronic pharyngitis
M0...00	Skin and subcutaneous tissue infections
A41..00	Slow viral central nervous system infection

AD62.00	Specific infections by free-living amoebae
A79..00	Specific viral infections
4E3Z.11	Sputum evidence of infection
A3B1.00	Staphylococcal infection
F003.00	Staphylococcal meningitis
A381.00	Staphylococcal septicaemia
A3B0.00	Streptococcal infection
F002.00	Streptococcal meningitis
A340200	Streptococcal pharyngitis
A3C0.11	Streptococcal sepsis
A3C0z00	Streptococcal sepsis, unspecified
A380.00	Streptococcal septicaemia
A412.00	Subacute sclerosing panencephalitis
F033111	Syphilis encephalitis
A94y000	Syphilitic encephalitis
A942.00	Syphilitic meningitis
AC32.00	Taenia saginata infection
H02..13	Throat infection - pharyngitis
H03..11	Throat infection - tonsillitis
A63..00	Tick-borne viral encephalitis
A63z.00	Tick-borne viral encephalitis NOS
AD00.00	Toxoplasma meningoencephalitis
F033411	Toxoplasmosis encephalitis
H053.00	Tracheopharyngitis
H5y0100	Tracheostomy sepsis
AC1z.00	Trematode infection NOS
A97..12	Treponemal infection
F032111	Trypanosomiasis encephalitis
F033311	Tuberculous encephalitis
A136000	Tuberculous encephalitis
A136.00	Tuberculous encephalitis or myelitis
A136z00	Tuberculous encephalitis or myelitis NOS
N22yD00	Tuberculous infection of tendon sheath
A130200	Tuberculous leptomeningitis
A130.00	Tuberculous meningitis
A130z00	Tuberculous meningitis NOS
A130300	Tuberculous meningoencephalitis
A116.00	Tuberculous pneumonia
A075.00	Unspecified bacterial enteritis
F033z00	Unspecified encephalitis due to other infection EC
AB40000	Unspecified histoplasma capsulatum infection
AB41000	Unspecified histoplasma duboisii infection
AB4z.00	Unspecified histoplasmosis infection
AB4z000	Unspecified histoplasmosis infection
F02z.00	Unspecified meningitis
F007z00	Unspecified meningitis in bacterial disease EC
AD6z.00	Unspecified other infectious and parasitic diseases
AD6zW00	Unspecified parasitic disease
H05z.00	Upper respiratory infection NOS
K190500	Urinary tract infection
K190.00	Urinary tract infection, site not specified

Appendix 6-1m: Read codes used to identify people with electrolyte imbalance

Read codes	**Electrolyte description**
C36..00	Disorders of fluid, electrolyte and acid-base balance

C36z.00	Disorders of fluid, electrolyte and acid-base balance NEC
SLE5.00	Electrolyte agent poisoning
C36..11	Electrolyte disorders
C36zz00	Electrolyte imbalance NOS
8897.11	Electrolyte regulation
44I3.00	Electrolytes abnormal
C36z200	Fluid imbalance
C367.00	Hyperkalaemia
C368.00	Hypokalaemia
C361.11	Hyponatraemia
C361.00	Hyposmolality and or hyponatraemia
44IZ.00	Serum electrolytes NOS
4412100	Urea and electrolytes abnormal
46M2.00	Urine electrolytes abnormal
Cyu8M00	[X]Other electrolyte+fluid disorders,NEC

Appendix 6-1n: Read codes used to identify people with postural hypotension

Read codes	Postural hypotension Read code descriptions
G871.00	Chronic hypotension
1B55.00	Dizziness on standing up
14AS.00	History of hypotension
G87..00	Hypotension
G87z.00	Hypotension NOS
G872.00	Idiopathic hypotension
2468.00	O/E - BP reading:postural drop
G870.00	Orthostatic hypotension
F130300	Parkinsonism with orthostatic hypotension
G870.11	Postural hypotension
R1y3.00	[D]Low blood pressure reading
Gyu9000	[X]Other hypotension

Appendix 6-1o: Read codes used to identify PD recording

Read codes	Parkinson’s disease symptom Read code descriptions
F12..00	Parkinson's disease
F12z.00	Parkinson's disease NOS
F130300	Parkinsonism with orthostatic hypotension
Eu02300	[X]Dementia in Parkinson's disease

Appendix 6-1p: Read codes used to identify people with surgical reasons.

Read codes	**Surgical reasons Read code descriptions**
22QA.00	Surgical wound
3511.00	Surgical biopsy taken
3513.00	Surgical biopsy normal
3514.00	Surgical biopsy abnormal
6AD..00	Surgical review
6AD0.00	Minor surgery post-op review

7....12	Surgical procedures
7008600	Stereotactic radiosurgery on tissue of brain
7020.11	Microsurgical graft to cranial nerve
7020000	Primary microsurgical graft to facial nerve (VII)
7020100	Secondary microsurgical graft to facial nerve (VII)
7020200	Microsurgical graft to facial nerve (VII) NEC
7020300	Primary microsurgical graft to cranial nerve NEC
7020400	Secondary microsurgical graft to cranial nerve NEC
7020500	Microsurgical graft to cranial nerve NEC
7053.00	Microsurgical repair of peripheral nerve
7053000	Primary microsurgical graft to peripheral nerve
7053100	Secondary microsurgical graft to peripheral nerve
7053200	Microsurgical graft to peripheral nerve NEC
7053300	Primary microsurgical repair of peripheral nerve NEC
7053400	Secondary microsurgical repair of peripheral nerve NEC
7053500	Microsurgical graft to multiple peripheral nerves NEC
7053600	Microsurgical repair of multiple peripheral nerves NEC
7053y00	Other specified microsurgical repair of peripheral nerve
7053z00	Microsurgical repair of peripheral nerve NOS
7211600	Cryosurgical destruction of lesion of canthus
7247000	Surgical removal of foreign body from cornea
7254100	Surgical iridectomy
7257100	Surgical iridotomy
7259.00	Operations following glaucoma surgery
7259000	Needling of bleb following glaucoma surgery
7259100	Injection of bleb following glaucoma surgery
7259200	Revision of bleb NEC following glaucoma surgery
7259300	Removal of releasable suture following glaucoma surgery
7259400	Laser suture lysis following glaucoma surgery
7259y00	Other specified operations following glaucoma surgery
7259z00	Operations following glaucoma surgery NOS
7268300	Surgical removal of foreign body from lens
7403900	Surgical outfracture of turbinate of nose
7404.00	Surgical arrest of bleeding from internal nose
7404y00	Surgical arrest of bleeding from internal nose OS
7404z00	Surgical arrest of bleeding from internal nose NOS
7406800	Surgical closure of anterior nares
7406900	Surgical reopening of anterior nares
7421300	Surgical arrest of postoperative bleeding of adenoid
7426700	Cryosurgery to pharyngeal lymphatic tissue
7511.00	Surgical removal of tooth
7511000	Surgical removal of impacted wisdom tooth
7511100	Surgical removal of impacted tooth NEC
7511200	Surgical removal of wisdom tooth NEC
7511300	Surgical removal of tooth NEC
7511400	Surgical removal of retained root of tooth
7511y00	Other specified surgical removal of tooth
7511z00	Surgical removal of tooth NOS
7513.00	Preprosthetic oral surgery
7513y00	Other specified preprosthetic oral surgery
7513z00	Preprosthetic oral surgery NOS
7517500	Surgical arrest of postoperative bleeding from tooth socket
7531400	Surgical arrest of postoperative bleeding from tonsillar bed
7A52500	Microsurgical repair artery
7A6D600	Microsurgical repair vein
7B07.00	Percutaneous renal stone surgery
7B07y00	Other specified percutaneous renal stone surgery
7B07z00	Percutaneous renal stone surgery NOS

7C00300	Cryosurgical destruction of lesion of scrotum
7C10D00	Microsurgical epididymovasostomy
7C10E00	Non-microsurgical epididymovasostomy
7C12200	Microsurgical reversal of vasectomy
7C12300	Non-microsurgical reversal of vasectomy
7C26411	Microsurgical epididymal sperm aspiration
7D03200	Cryosurgery of lesion of vulva
7D06200	Cryosurgery to lesion of female perineum
7M0L000	Surgical removal of foreign body from organ NOC
7M1B000	Functional endoscopic sinus surgery
7M1B100	Functional endoscopic nasal surgery
7P23.00	Rehabilitation for trauma and reconstructive surgery
7P23100	Del rehab following other plastic reconstructive surgery NEC
7P23y00	OS rehabilitation for trauma and reconstructive surgery
7P23z00	Rehabilitation for trauma and reconstructive surgery NOS
8C1M.11	Post-surgical wound care
8CAx.00	Advised about minor surgery post-operative self care
8F81.00	Convalescence after surgery
8H22.00	Admit surgical emergency unsp.
8H2I.00	Admit plastic surgery emergenc
8H2K.00	Admit oral surgical emergency
8H2N.00	Admit neurosurgical emergency
8H2W.00	Admit vascular surgery emergency
8H37.00	Non-urgent surgical admission
8H3S.00	Non-urgent neurosurgical admission
8HB3.00	Surgical follow-up
8HB3000	Surgical follow-up - normal
8HBL.00	Minor surgery follow-up arrang
8HLG.00	General surgical D.V. done
8HLL.00	Neurosurgical D.V. done
8HLM.00	Paediatric surgical D.V. done
8HLP.00	Plastic surgery D.V. done
8HLQ.00	Oral surgery D.V. done
8HLS.00	Other surgical D.V. done
8P...00	Removal of surgical material and sutures
9871.00	Minor surgery done + claimable
9876.00	Minor surgery done - cautery
9877.00	Minor surgery done - injection
9878.00	Minor surgery done -aspiration
9879.00	Minor surgery done - incision
987B.00	Minor surgery done - other
987C.00	Minor surgery done
987Z.00	FP/MS -minor surgery claim NOS
98CO.00	GMS4 claim - minor surgery signed
98CP.00	GMS4 claim - minor surgery sent to HA
98CQ.00	GMS4 claim - minor surgery paid
98CR.00	GMS4 claim - minor surgery returned unpaid
9b80.00	General surgery
9b85.00	Oral surgery
9b89.00	Neurosurgery
9b8A.00	Plastic surgery
9b8B.00	Cardiothoracic surgery
9b8B000	Cardiac surgery
9b8B100	Thoracic surgery
9b8C.00	Paediatric surgery
9b8G.00	Hepatobiliary and pancreatic surgery
9b8H.00	Breast surgery
9b8J.00	Colorectal surgery

9b8K.00	Transplantation surgery
9b8L.00	Maxillofacial surgery
9b8M.00	Upper gastrointestinal surgery
9b8N.00	Vascular surgery
9c05300	Acute surgical intervention on development of symptoms
C171000	Postsurgical testicular hypofunction
F291.00	Nervous system complication from surgically implanted device
F446200	Surgical implantation cyst
F4B4B00	Keratopathy following cataract surgery
F4B4C00	Bullous aphakic keratopathy following cataract surgery
F4G4800	Orbit deformity due to surgery
F4G5300	Enophthalmos due to surgery
F4K2D00	Vitreous syndrome following cataract surgery
Gyu9100	[X]Other functional disturbances following cardiac surgery
H585100	Pulmonary insufficiency following surgery
Hy00.00	Acute pulmonary insufficiency following thoracic surgery
Hy01.00	Acute pulmonary insufficiency following nonthoracic surgery
Hy02.00	Chronic pulmonary insufficiency following surgery
J522.00	Postgastric surgery syndromes
J522z00	Postgastric surgery syndrome NOS
J523.00	Vomiting after gastrointestinal tract surgery
J524.00	Other post gastrointestinal tract surgery disorder
J524000	Diarrhoea after gastrointestinal tract surgery
J524z00	Other post gastrointestinal tract surgery disorder NOS
J693.00	Other postsurgical nonabsorption
J693.11	Postsurgical malabsorption - other
J693000	Post gastrointestinal tract surgery hypoglycaemia
J693100	Post gastrointestinal tract surgery malnutrition
J693z00	Postsurgical nonabsorption NOS
N12A.11	Post spinal surgery syndrome
N330700	Postsurgical malabsorption osteoporosis
N331400	Postsurgical malabsorption osteoporosis with path fracture
N372200	Other post-surgical lordosis
N373800	Post-surgical scoliosis
SC43.00	Late effect of medical and surgical care complication
SC43.12	Late effect of surgical care complication
SP...00	Surgical and medical care complications NEC
SP01600	Mechanical complication of arterio-venous surgical shunt
SP01700	Mechanical complication of arterio-venous surgical fistula
SP2..12	Surgical complication NEC
SP22000	Injury to blood vessel during surgery
SP22100	Injury to nerve during surgery
SP22300	Injury to viscus during surgery
SP23200	Surgical wound necrosis
SP23z11	Delayed healing surgical wound
SP23z12	Healing delayed surgical wound
SP23z13	Wound surgical healing delayed
SP2y000	Surgical emphysema
SP31100	Air embolism due to surgery
SPz..00	Medical and surgical care complications NOS
SyuK.00	[X]Complications of surgical and medical care, NEC
SyuLA00	[X]Sequelae of complication of surgical & medical care, NEC
TA...00	Medical accidents to patients during surgical/medical care
TA00.00	Accid cut,puncture,perf,h'ge - surgical operation
TA10.00	Foreign object left in body during surgical operation
TA20.00	Failure of sterile precautions during surgical operation
TA40.00	Mechanical failure of apparatus - surgical operation
TAy2.00	Failure in suture and ligature during surgical operation

TAy2000	Suture failure during surgical operation
TAy2100	Ligature failure during surgical operation
TAy2z00	Suture or ligature failure during surgical operation NOS
TB...00	Medical + surgical procedures causing complications,no blame
TB0..00	Surgical procedures causing complications, without blame
TB04.00	Other restorative surgery with complication, without blame
TB0y.00	Other surgical operations/procedures+complication, no blame
TB0z.00	Surgical operations/procedures + complication, no blame, NOS
U6...00	[X]Complications of medical and surgical care
U61..00	[X]Misadventures to patients during surgical + medical care
U610000	[X]Unintent cut/puncture/perf/haemorrh during surgical opn
U612000	[X]Failure of sterile precautions during surgical operation
U613.00	[X]Failure in dosage during surgical and medical care
U613y00	[X]Failure in dosage during other surgical and medical care
U613z00	[X]Failure in dosage during unspec surgical + medical care
U615.00	[X]Other misadventures during surgical and medical care
U615100	[X]Wrong fluid used in infusn during surgical+medical care
U615200	[X]Failure in suture or ligature during surgical operation
U615y00	[X]Other specified misadvents dur surgical + medical care
U61z.00	[X]Unspecified misadventure during surgical and medical car
U62B.00	[X]General/plastic surgery device assoc with advers incident
Z174O00	Post-surgical wound care
Z1R3200	Surgical debridement of wound
ZV45.00	[V]Other postsurgical states
ZV45y00	[V]Other specified postsurgical state
ZV45z00	[V]Unspecified postsurgical state
ZV50.11	[V]Elective cosmetic surgery
ZV50100	[V]Other cosmetic plastic surgery
ZV50y00	[V]Other specified elective cosmetic or ritual surgery
ZV50z00	[V]Unspecified elective cosmetic or ritual surgery
ZV51.00	[V]Plastic surgery used in aftercare
ZV57600	[V]Rehabilitation following surgery
ZV58300	[V]Attention to surgical dressings or sutures
ZV58311	[V]Attention to surgical dressing
ZV58400	[V]Other aftercare following surgery
ZV5A.00	[V]Prophylactic surgery
ZV5A000	[V]Prophyl surgery for risk-factors related to mal neoplasms
ZV5Ay00	[V]Other prophylactic surgery
ZV5Az00	[V]Prophylactic surgery, unspecified
ZV64100	[V]Surgical/other procedure not carried out-contraindication
ZV66000	[V]Convalescence after surgery
ZV67000	[V]Surgical follow-up
ZV6C.00	[V]Follow-up care involving plastic surgery
ZV6C000	[V]Follow-up care involving plastic surgery of head and neck
ZV6C100	[V]Follow-up care involving plastic surgery of breast
ZV6C200	[V]Follow-up care involv plastic surgery oth parts of trunk
ZV6C500	[V]Follow-up care involv plastic surgery of other body part
ZVu3000	[X]Other prophylactic surgery
ZVu3100	[X]Other plastic surgery for unacceptable cosmet appearance
ZVu3500	[X]Follow-up care involv plastic surgery of other body part
ZVu3F00	[X]Other specified surgical follow-up care
ZVu6l00	[X]Other specified postsurgical states

Appendix 6-1q: Read codes used to identify people with recording of cardiovascular diseases.

Read codes	**Cardiovascular Read code descriptions**

1477.00	H/O: cerebrovascular disease
14A..00	H/O: cardiovascular disease
14A3.00	H/O: myocardial infarct <60
14A4.00	H/O: myocardial infarct >60
14A5.00	H/O: angina pectoris
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
14AA.00	H/O: heart disease NOS
14AB.00	H/O: TIA
14AH.00	H/O: Myocardial infarction in last year
14AJ.00	H/O: Angina in last year
14AK.00	H/O: Stroke in last year
14AL.00	H/O: Treatment for ischaemic heart disease
14AT.00	History of myocardial infarction
14AZ.00	H/O: CVS disease NOS
322..00	ECG: myocardial ischaemia
3222.00	ECG:shows myocardial ischaemia
322Z.00	ECG: myocardial ischaemia NOS
323..00	ECG: myocardial infarction
3232.00	ECG: old myocardial infarction
3233.00	ECG: antero-septal infarct.
3234.00	ECG:posterior/inferior infarct
3235.00	ECG: subendocardial infarct
3236.00	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
792..00	Coronary artery operations
792..11	Coronary artery bypass graft operations
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery
7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery
7922100	Allograft replacement of two coronary arteries

7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923.00	Prosthetic replacement of coronary artery
7923.11	Prosthetic bypass of coronary artery
7923000	Prosthetic replacement of one coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924500	Revision of implantation of thoracic artery into heart
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925011	LIMA sequential anastomosis
7925012	RIMA sequential anastomosis
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925311	LIMA single anastomosis
7925312	RIMA single anastomosis
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928.00	Transluminal balloon angioplasty of coronary artery
7928.11	Percutaneous balloon coronary angioplasty
7928000	Percut transluminal balloon angioplasty one coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928300	Percut translum cutting balloon angioplasty coronary artery
7928y00	Transluminal balloon angioplasty of coronary artery OS

7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929.00	Other therapeutic transluminal operations on coronary artery
7929000	Percutaneous transluminal laser coronary angioplasty
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929500	Insertion of drug-eluting coronary artery stent
7929600	Percutaneous transluminal atherectomy of coronary artery
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792A.00	Diagnostic transluminal operations on coronary artery
792Ay00	Diagnostic transluminal operation on coronary artery OS
792Az00	Diagnostic transluminal operation on coronary artery NOS
792B.00	Repair of coronary artery NEC
792B000	Endarterectomy of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
793G.00	Perc translumin balloon angioplasty stenting coronary artery
793G000	Perc translum ball angio insert 1-2 drug elut stents cor art
793G100	Perc tran ball angio ins 3 or more drug elut stents cor art
793G200	Perc translum balloon angioplasty insert 1-2 stents cor art
793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC
793Gy00	OS perc translumina balloon angioplast stenting coronary art
793Gz00	Perc translum balloon angioplasty stenting coronary art NOS
793H.00	Transluminal operations on cardiac conduit
793H000	Percutaneous transluminal balloon dilation cardiac conduit
7A54500	Rotary blade angioplasty
7A6G100	Peroperative angioplasty
7A6H300	Prosthetic graft patch angioplasty
7A6H400	Percutaneous transluminal angioplasty of vascular graft
7P24000	Delivery of rehabilitation for acute cardiac disorders
7P24200	Delivery of rehabilitation for stroke
8CRB.00	Transient ischaemic attack clinical management plan
8H2V.00	Admit ischaemic heart disease emergency
8HBJ.00	Stroke / transient ischaemic attack referral
8HHM.00	Ref to multidisciplinary stroke function improvement service
8HTQ.00	Referral to stroke clinic
9N0p.00	Seen in stroke clinic
9N4X.00	DNA - Did not attend stroke clinic
F423600	Amaurosis fugax
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease

G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease

G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI

G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
G501.00	Post infarction pericarditis
G6...00	Cerebrovascular disease
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction

G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G679.00	Small vessel cerebrovascular disease
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G681.00	Sequelae of intracerebral haemorrhage

G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Gyu6.00	[X]Cerebrovascular diseases
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6A00	[X]Other cerebrovascular disorders in diseases CE
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6D00	[X]Sequelae/other + unspecified cerebrovascular diseases
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
SP07600	Coronary artery bypass graft occlusion
ZLEP.00	Discharge from stroke serv
ZV12511	[V]Personal history of stroke
ZV45700	[V]Presence of aortocoronary bypass graft
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS

Appendix 6-2 to 6-7: Supplementary tables and figures for Incidence of hospitalisation in PD.

Appendix 6-2: Table 6-5: Crude incidence rates of hospital admissions among people with PD and Non-PD control cohort.

	Parkinson's disease cohort			Non-Parkinson's disease control cohort		
Variables	Events	Person-Years (1000)	Incidence rate (95% CI)	Events	Person-Years (1000)	Incidence rate (95% CI)
Overall	3,857	26.39	146.15 (141.61 to 150.84)	15,741	144.43	108.98 (107.29 to 110.70)
Age group						
50 to 59	183	1.70	107.35 (92.87 to 124.09)	574	9.49	60.51 (55.76 to 65.67)
60 to 69	692	5.95	116.38 (108.02 to 125.38)	2546	32.30	78.82 (75.82 to 81.94)
70 to 79	1570	11.03	142.35 (135.48 to 149.57)	6195	59.39	104.32 (101.75 to 106.95)
80 t0 89	1273	7.02	181.45 (171.75 to 191.70)	5680	39.22	144.83 (141.12 to 148.65)
>90	139	0.69	202.08 (171.13 to 238.63)	746	4.04	184.49 (171.71 to 198.21)
Gender						
Male	2343	15.89	147.48 (141.63 to 153.58)	9533	86.54	110.16 (107.97 to 112.39)
Female	1514	10.50	137.06 (137.06 to 151.58)	6208	57.89	107.23 (104.60 to 109.93)
Year						
2006	80	0.44	180.08 (144.64 to 224.20)	313	2.22	140.98 (126.20 to 157.50)
2007	211	1.20	175.76 (153.58 to 201.15)	752	5.91	127.32 (118.54 to 136.75)
2008	317	1.86	170.25 (152.50 to 190.06)	1196	8.74	136.81 (129.27 to 144.78)
2009	390	2.38	164.09 (148.59 to 181.21)	1459	11.03	132.26 (125.64 to 139.22)
2010	412	2.72	151.44 (137.50 to 166.79)	1571	12.97	121.12 (115.28 to 127.26)
2011	461	2.98	154.53 (141.05 to 169.30)	1706	15.24	111.94 (106.75 to 117.38)
2012	458	3.18	143.90 (131.30 to 157.70)	1973	17.35	113.74 (108.83 to 118.87)
2013	421	3.24	129.96 (118.12 to 142.99)	1914	18.66	102.56 (98.07 to 107.26)
2014	453	3.21	141.15 (128.73 to 154.76)	1923	19.47	98.76 (94.45 to 103.28)
2015	409	2.81	145.68 (132.22 to 160.50)	1606	17.59	91.33 (86.97 to 95.90)
2016	245	2.36	103.65 (91.45 to 117.47)	1328	15.26	87.03 (82.47 to 91.84)
Townsend quintile						
1 (least deprived)	1089	7.57	143.84 (135.55 to 152.65)	3938	37.03	106.34 (103.07 to 109.72)
2	924	6.16	150.0 (140.63 to 159.99)	3471	32.03	105.42 (101.97 to 108.99)
3	702	4.87	144.25 (133.96 to 155.32)	3066	28.13	109.0 (105.21 to 112.93)
4	532	3.73	142.74 (131.11 to 155.40)	2511	21.67	115.87 (111.43 to 120.49)
5 (most deprived)	340	2.18	156.04 (140.30 to 173.54)	1547	14.24	108.67 (103.39 to 114.22)
No records	270			1208		
Urban-rural 1						
1 = Urban >10k-Sparce	4	0.02	197.17 (74.0 to 525.33)	4	0.19	21.35 (8.01 to 56.88)
2 = Town & Fringe-Sparce	29	0.24	120.48 (83.73 to 173.38)	96	1.16	82.61 (67.63 to 100.90)
3 = Village, Hamlet, & Isolated dwellings - Sparce	19	0.18	105.66 (67.40 to 165.65)	79	0.92	85.72 (68.76 to 106.87)

4 = Urban > 10k – Less sparse	2265	14.84	152.66 (146.50 to 159.07)	9308	81.19	114.65 (112.34 to 117.0)
5 = Town & Fringe – Less sparse.	387	2.49	155.70 (140.94 to 172.01)	1545	13.51	114.39 (108.83 to 120.24)
6 = Village, Hamlet & Isolated dwellings – Less sparse.	230	1.51	152.07 (133.64 to 173.05)	869	13.50	116.48 (108.99 to 124.49)
No records	923			3840	7.46	
Urban-rural 2						
Urban	2269	14.86	152.72 (146.56 to 159.13)	9312	81.38	114.43 (112.13 to 116.78)
Town	416	2.73	152.59 (138.61 to 167.99)	1641	14.67	111.86 (106.59 to 117.42)
Rural	249	1.69	147.14 (129.95 to 166.60)	948	8.38	113.10 (106.13 to 120.54)
No records	923			3840		
UK Countries						
England	2736	17.73	154.28 (148.61 to 160.17)	11,276	97.17	116.04 (113.92 to 118.21)
Northern Ireland	248	1.25	197.99 (174.82 to 224.23)	988	7.76	127.38 (119.68 to 135.58)
Wales	471	4.48	105.02 (95.96 to 114.95)	1893	24.19	78.26 (74.82 to 81.87)
Scotland	402	2.91	137.71 (124.89 to 151.86)	1584	15.32	103.39 (98.42 to 108.61)
UK Regions						
East Midlands	46	0.44	103.57 (77.57 to 138.27)	189	2.12	89.01 (77.19 to 102.65)
East of England	254	1.51	168.37 (148.89 to 190.40)	986	8.10	121.72 (114.35 to 129.56)
London	359	2.44	147.22 (132.75 to 163.27)	1507	13.59	110.92 (105.46 to 116.66)
North East	64	0.59	107.86 (84.42 to 137.80)	280	3.08	90.94 (80.89 to 102.25)
North West	367	2.33	157.49 (142.17 to 174.45)	1573	13.24	118.78 (113.06 to 124.80)
Northern Ireland	248	1.25	197.99 (174.82 to 224.23)	988	7.76	127.38 (119.68 to 135.58)
Scotland	471	4.48	105.02 (95.96 to 114.95)	1893	24.19	78.26 (74.82 to 81.87)
South Central	454	2.86	158.58 (144.65 to 173.86)	1925	15.35	125.39 (119.91 to 131.12)
South East Coast	457	3.09	147.88 (134.93 to 162.08)	1898	16.90	112.34 (107.40 to 117.51)
South West	369	2.13	173.54 (156.71 to 192.18)	1431	11.80	121.22 (115.10 to 127.67)
Wales	402	2.92	137.71 (124.89 to 151.86)	1584	15.32	103.39 (98.42 to 108.61)
West Midlands	292	1.97	148.48 (132.39 to 166.53)	1212	10.74	112.84 (106.67 to 119.38)
Yorkshire and Humber	74	0.37	198.38 (157.96 to 249.15)	275	2.25	122.45 (108.80 to 137.81)

Appendix 6-3: Table 6-6: Adjusted rates of hospital admissions (adjusted for age, gender, calendar year, social deprivation and smoking) following PD diagnosis/index date for non-PD cohort.

Variables	PD cohort				Non-PD cohort						
	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Incidence rate ratio	**p-value	***p-value
Years since diagnosis/index date											
First year	1,220	8.75	132.94 (124.74 to 141.14)	<0.001	5,312	46.49	109.91 (105.64 to 114.16)	<0.001	1.21 (1.14 to 1.29)	<0.001	<0.001
Second year	849	6.28	132.63 (122.96 to 142.30)		3,424	32.70	104.05 (99.20 to 108.90)		1.27 (1.19 to 1.37)	<0.001	
Third year	615	4.36	142.58 (129.97 to 155.19)		2,436	23.09	107.48 (101.82 to 113.13)		1.32 (1.21 to 1.45)	<0.001	
Fourth year	455	2.89	163.81 (146.50 to 181.12)		1,613	15.90	105.43 (98.62 to 112.24)		1.55 (1.40 to 1.72)	<0.001	
Fifth year	319	1.83	187.78 (166.50 to 209.07)		1,183	10.69	117.03 (108.50 to 125.57)		1.60 (1.42 to 1.81)	<0.001	
Sixth year	193	1.20	195.84 (167.35 to 224.32)		741	6.88	116.06 (105.52 to 126.60)		1.69 (1.45 to 1.97)	<0.001	
Seventh year	104	0.62	193.04 (154.28 to 231.80)		501	4.22	131.08 (116.72 to 145.44)		1.47 (1.19 to 1.82)	<0.001	
Eighth year	102	0.54	226.55 (183.02 to 270.07)		531	4.46	135.79 (121.58 to 150.00)		1.67 (1.35 to 2.06)	<0.001	

Appendix 6-4: Table 6-7: Adjusted incidence rates and ratios of hospital admissions by age group and gender.

Variables	Parkinson's disease group				Non-Parkinson's disease control group						
	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Incidence rate ratio	**p-value	***p-value
Age group											
50 to 59	183	1.70	106.11 (90.03 to 122.19)	<0.001	574	9.49	60.33 (54.80 to 65.86)	<0.001	1.75 (1.49 to 2.06)	<0.001	<0.001
60 to 69	692	5.95	115.77 (106.38 to 125.16)		2546	32.30	79.18 (75.09 to 83.26)		1.46 (1.35 to 1.58)	<0.001	
70 to 79	1570	11.03	141.76 (133.64 to 149.87)		6195	59.39	105.17 (100.77 to 109.58)		1.34 (1.28 to 1.41)	<0.001	
80 to 89	1273	7.02	181.40 (170.53 to 192 .27)		5680	39.22	147.22 (141.01 to 153.43)		1.23 (1.16 to 1.30)	<0.001	
>90	139	0.69	199.69 (167.29 to 232.09)		746	4.04	188.51 (171.58 to 205.45)		1.06 (0.89 to 1.26)	0.517	
Gender											
Male	2,343	15.89	149.24 (141.75 to 156.73)	0.1299	9,533	86.54	113.27 (108.95 to 117.59)	0.0015	1.32 (1.27 to 1.38)	<0.001	0.992
Female	1,514	10.50	142.36 (134.15 to 150.57)		6,208	57.89	106.92 (102.46 to 111.37)		1.32 (1.26 to 1.39)	<0.001	

*Adjusted for age, gender and calendar year. **Wald test for categorical variables. ***Wald test for multiplicative interaction.

Appendix 6-5: Table 6-8: Adjusted incidence rates and ratios of hospital admissions by age group, gender and social deprivation.

Variables	Parkinson's disease group				Non-Parkinson's disease control group						
	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	**p-value	Incidence rate ratio	**p-value	***p-value
Age group											
50 to 59	183	1.70	106.24 (90.18 to 122.31)	<0.001	574	9.49	60.30 (54.77 to 65.83)	<0.001	1.75 (1.49 to 2.06)	<0.001	<0.001
60 to 69	692	5.95	115.81 (106.42 to 125.20)		2546	32.30	79.25 (75.16 to 83.33)		1.46 (1.35 to 1.58)	<0.001	
70 to 79	1570	11.03	141.89 (133.76 to 150.02)		6195	59.39	105.20 (100.79 to 109.60)		1.34 (1.28 to 1.42)	<0.001	
80 to 89	1273	7.02	181.36 (170.47 to 192.26)		5680	39.22	147.11 (140.91 to 153.31)		1.23 (1.16 to 1.30)	<0.001	
>90	139	0.69	199.22 (166.89 to 231.56)		746	4.04	188.36 (171.47 to 205.26)		1.06 (0.89 to 1.26)	0.493	
Gender											
Male	2343	15.89	149.26 (141.78 to 156.74)	0.1327	9533	86.54	113.36 (109.04 to 117.68)	0.0010	1.33 (1.27 to 1.38)	<0.001	0.976
Female	1514	10.50	142.44 (134.23 to 150.66)		6208	57.89	106.80 (102.36 to 111.24)		1.32 (1.26 to 1.39)	<0.001	
Townsend quintile											
1(least deprived)	1089	7.57	145.31 (134.82 to 155.81)	0.8562	3938	37.03	109.29 (104.03 to 114.54)	0.0173	1.34 (1.26 to 1.42)	<0.001	0.117
2	924	6.16	149.47 (139.09 to 159.85)		3471	32.03	106.24 (101.01 to 111.46)		1.40 (1.30 to 1.51)	<0.001	
3	702	4.87	145.13 (133.81 to 156.45)		3066	28.13	110.47 (104.64 to 116.29)		1.32 (1.22 to 1.42)	<0.001	
4	532	3.73	142.77 (130.02 to 155.51)		2511	21.67	116.16 (109.97 to 122.34)		1.23 (1.12 to 1.34)	<0.001	
5(most deprived)	340	2.18	153.57 (136.45 to 170.71)		1547	14.24	110.81 (103.55 to 118.06)		1.38 (1.23 to 1.53)	<0.001	
No records	270				1208						

*Adjusted for age, gender, calendar year and social deprivation **Wald test for categorical variables. ***Wald test for multiplicative interaction.

Appendix 6-6: Table 6-9: Adjusted incidence rates and ratios of hospital admissions by age group, gender, calendar year, social deprivation and smoking.

Variables	Parkinson's disease group				Non-Parkinson's disease control group						
	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	p-value	Events	Person-Years (1000)	*Adjusted Incidence rate (95% CI)	p-value	Incidence rate ratio	**p-value	***p-value
Age group											
50 to 59	183	1.70	107.98 (91.61 to 124.36)	<0.001	574	9.49	60.34 (54.78 to 65.90)	<0.001	1.78 (1.51 to 2.09)	<0.001	<0.001
60 to 69	692	5.95	117.23 (107.71 to 126.75)		2546	32.30	78.97 (74.88 to 83.06)		1.48 (1.37 to 1.61)	<0.001	
70 to 79	1570	11.03	142.79 (134.64 to 150.94)		6195	59.39	104.74 (100.36 to 109.12)		1.36 (1.29 to 1.43)	<0.001	
80 to 89	1273	7.02	183.09 (172.09 to 194.10)		5680	39.22	147.56 (141.33 to 153.78)		1.24 (1.17 to 1.31)	<0.001	
>90	139	0.69	202.80 (169.81 to 235.78)		746	4.04	191.87 (174.47 to 209.27)		1.06 (0.89 to 1.26)	0.492	
Gender											
Male	2343	15.89	149.21 (141.77 to 156.66)	0.3165	9533	86.54	112.37 (108.07 to 116.66)	0.0319	1.34 (1.28 to 1.39)	<0.001	0.932
Female	1514	10.50	145.71 (137.27 to 154.14)		6208	57.89	107.93 (103.42 to 112.43)		1.34 (1.27 to 1.41)	<0.001	
Townsend quintile											
1(least deprived)	1089	7.57	147.87 (137.15 to 158.59)	0.8237	3938	37.03	110.38 (105.06 to 115.69)	0.0447	1.35 (1.26 to 1.43)	<0.001	0.087
2	924	6.16	151.83 (141.30 to 162.36)		3471	32.03	106.49 (101.26 to 111.72)		1.42 (1.32 to 1.53)	<0.001	
3	702	4.87	146.05 (134.68 to 157.41)		3066	28.13	110.27 (104.44 to 116.09)		1.33 (1.23 to 1.43)	<0.001	
4	532	3.73	142.84 (130.07 to 155.62)		2511	21.67	115.03 (108.90 to 121.17)		1.24 (1.13 to 1.36)	<0.001	
5(most deprived)	340	2.18	152.72 (135.63 to 169.81)		1547	14.24	108.49 (101.36 to 115.61)		1.40 (1.25 to 1.55)	<0.001	
No records	270				1208						

*Adjusted for age, gender, calendar year, social deprivation and smoking. **Wald test for categorical variables. ***Wald test for multiplicative interaction

Appendix 6-7: Table 6-10: Reasons for hospital admissions among those admitted.

	Parkinson's disease cohort			Non-Parkinson's disease control cohort				
Reasons for hospital admission	Number admitted	%	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Number admitted	%	Rate admitted for the reason per 1,000 person-years (95% Confidence Interval)	Incidence rate ratio (95% Confidence Interval)	*p-value
Neuropsychiatric complications (psychosis and hallucinations)	138	3.58	5.23 (4.43 to 6.18)	97	0.62	0.67 (0.55 to 0.82)	7.79 (6.01 to 10.10)	<0.001
Dementia	282	4.15	15.73 (14.28 to 17.31)	688	1.18	4.50 (4.17 to 4.86)	3.49 (3.06 to 3.99)	<0.001
Myocardial infarction/Ischaemic heart disease	86	2.23	3.26 (2.64 to 4.03)	569	3.61	3.90 (3.59 to 4.23)	0.84 (0.67 to 1.04)	0.112
Congestive heart failure	95	2.46	3.60 (2.94 to 4.40)	649	4.12	3.60 (2.94 to 4.40)	0.80 (0.64 to 1.01)	0.056
Stroke	168	4.36	6.33 (5.44 to 7.36)	698	4.43	4.80 (4.46 to 5.18)	1.32 (1.12 to 1.54)	0.001
Hypertension	92	2.39	3.49 (2.84 to 4.28)	639	4.06	4.37 (4.04 to 4.72)	0.80 (0.64 to 1.0)	0.051
Gastrointestinal complications	417	10.81	15.80 (14.36 to 17.39)	1,330	8.45	9.21 (8.73 to 9.72)	1.72 (1.53 to 1.92)	<0.001
Falls	517	13.40	19.59 (17.97 to 21.35)	1,206	7.66	8.35 (7.89 to 8.83)	2.35 (2.12 to 2.60)	<0.001
Fractures	316	8.19	11.94 (10.69 to 13.33)	734	4.66	5.02 (4.67 to 5.41)	2.37 (2.07 to 2.72)	<0.001
Infections	444	11.51	16.82 (15.33 to 18.46)	1,623	10.31	11.23 (10.70 to 11.79)	1.50 (1.35 to 1.67)	<0.001
Recorded as cardiovascular causes	212	5.50	8.0 (6.99 to 9.15)	1,052	6.68	7.23 (6.81 to 7.69)	1.10 (0.95 to 1.28)	0.193
Cancer	250	6.48	9.47 (8.37 to 10.72)	1406	8.93	9.69 (9.20 to 10.21)	0.98 (0.85 to 1.12)	0.738
Postural hypotension	229	2.29	8.68 (7.62 to 9.88)	341	0.61	2.34 (2.10 to 2.60)	3.70 (3.14 to 4.37)	<0.001
Electrolyte imbalance	79	0.79	2.99 (2.40 to 3.73)	295	0.53	2.04 (1.82 to 2.29)	1.47 (1.14 to 1.88)	0.003
Parkinson's disease	177	4.59		NA	NA	NA	NA	NA
Surgical causes	273	2.73	10.31 (9.15 to 11.61)	1,107	1.99	7.66 (7.22 to 8.12)	1.35 (1.17 to 1.54)	<0.001
Not identified								

*****Unadjusted