Appendix C. Alzheimer's disease and mild cognitive impairment in UK general practice

A feasibility study

Summary

We conducted a feasibility study to identify the number of people with mild cognitive impairment or mild Alzheimer's disease using real-world data from general practices in England. This estimate is expected to help us understand the size of the population who may be eligible for a series of potentially disease-modifying treatments for Alzheimer's disease that are nearing the point of obtaining marketing authorisation and appraisal for use in the NHS by NICE.

A maximum of 80,000 people per year may have mild Alzheimer's disease, which approximates to a current prevalence of around 240,000 people, assuming a 3-year duration in mild illness. This prevalent population correlates closely with other estimates.

Background

A series of potentially disease-modifying treatments for Alzheimer's disease are nearing the point of obtaining marketing authorisation and appraisal for use in the NHS by NICE. These new drugs act by removing beta-amyloid and are only suitable for people with confirmed beta-amyloid deposits. This must be confirmed by PET imaging or cerebrospinal fluid testing.

Currently, Alzheimer's disease is primarily diagnosed by clinical features, meaning that the introduction of the new treatments also changes the diagnostic pathway in a substantial way. It is therefore important to understand the size of the population who may be eligible for screening (identifying beta-amyloid) and treatment.

The treatments furthest along the regulatory pathway in August 2023 are lecanemab and donanemab. A third drug, aducanemab, was approved in the

USA, but withdrew its European marketing authorisation application after an initial refusal of marketing authorisation.

Key trials of lecanemab and donanemab included people with early Alzheimer's disease in their screening population – that is, mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia (van Dyck et al. 2023, Sims et al. 2023). We aimed to identify the number of people likely to meet this description in UK general practice patient records.

Methods

Context

Our study was part of a wider project under NICE's HTA lab, which aims to identify issues that may complicate the technology appraisal process, allowing these issues to be addressed early and ultimately reduce delays in the technology appraisal.

The timescales for the HTA lab project meant that planning, conducting and reporting a full epidemiological study would not be possible. We therefore decided that a feasibility study was appropriate for this exploratory work.

We chose to use a primary care dataset, CPRD Aurum, because we expected that people with mild cognitive impairment and mild Alzheimer's disease may consult their GP but would not be likely to have been referred to secondary or tertiary care services at this stage of illness.

We understood from the outset that a feasibility study meant that estimates would be associated with several caveats, and options for refinement would be limited. However, we recognised that we would also gain insights into requirements for a full epidemiological study.

Defining the population

We identified 3 sets of codes that would help us to identify relevant patients. One set covered Alzheimer's disease and two sets covered mild cognitive impairment. See the code lists section at the end of this document for the final code lists used in the queries.

We were not able to identify any codes relating to beta-amyloid testing, so could not provide insight into this aspect of the pathway.

Incident and prevalent cases

We aimed to identify new (incident) cases that would give an estimate of the ongoing number of people who may present each year. We also aimed to identify prevalent cases, that is the whole population who may be eligible for treatment in the first year they are available. For prevalent cases, we assumed that mild Alzheimer's disease has a duration of 3 years. One important factor in this assumption is that the most recent 3 years of data available for analysis (April 2019 to March 2022) would be affected by changes to services to deal with COVID-19. The April 2016 to March 2019 period was therefore the most recent data available to best match the current clinical context.

Alzheimer's disease

We used the CPRD code searching tool to identify codes relating to diagnosis of Alzheimer's disease, selected the most relevant codes, and obtained clinical input on the selected codes.

We queried the data to identify new instances of these codes in each year, from 2013/14 to 2021/22. A key drawback of this strategy was that it did not allow us to detect mild-stage disease.

We set no age limits on Alzheimer's codes because we assumed that the number of inaccurate uses of these codes in younger patients would be small and would not substantially bias the results.

Mild cognitive impairment

To overcome the issue of unknown stage of disease at diagnosis, we looked to diagnosis of mild cognitive impairment as a step on the diagnostic path for Alzheimer's disease. However, mild cognitive impairment could be caused by several disease processes, such as thyroid dysfunction, menopause, Parkinson's disease, and non-Alzheimer's dementias.

We therefore sought to identify the number of people who had diagnoses of both mild cognitive impairment and Alzheimer's disease within a 3-year period. This would be our proxy for the mild phase of Alzheimer's disease.

We identified a set of codes relating to diagnosis of mild cognitive impairment using the CPRD code searching tool and also identified a set of cognitive impairment clinical finding codes produced by OpenSafely.

We expected that diagnosis of mild cognitive impairment could be under-reported because people might not present to their GP until they are having more troubling symptoms. The clinical finding codes aimed to identify additional people who might not yet have a formal diagnosis of mild cognitive impairment recorded. However, because the cognitive impairment findings may not represent mild findings, this could overestimate the population.

Clinical review of the clinical findings codes substantially reduced the number of included codes from the original OpenSafely set.

We restricted the age range of the mild cognitive impairment codes to 55 years and older because younger people with these codes would be less likely to develop Alzheimer's disease. We set the age limit based on clinical advice. The corresponding CPRD medical codes for the selected SNOMED codes were then identified, which further reduced the list of SNOMED codes as not all SNOMED codes have an equivalent or are used in CPRD Aurum. At the same time, for some SNOMED codes, the same SNOMED code is used for multiple CPRD Aurum medical codes.

Extrapolating to population estimates

Population coverage

Several factors affect the accuracy of extrapolating population coverage. First is that the number of practices contributing data to CPRD is always changing. Generally, more practices are contributing data over time, however a small number of practices stop contributing to the dataset.

The CPRD population grows each year, meaning that the proportion of the England population represented in CPRD differs from year to year. We account for the changing CPRD population by using the total number of alive and registered patients at the start of each year as the denominator for the incidence calculations and the equivalent but for the middle of the three year period for the prevalence calculations. Then, to estimate the equivalent number of cases in the England population, we apply the incidence or prevalence estimates from CPRD to the ONS estimate of the mid-2021 England population, which the ONS draws from the 2021 census.

Finally, over time the number of practices in Scotland, Wales and Northern Ireland contributing to CPRD Aurum has reduced considerably. By the March 2022 release, 99% of the data came from practices in England. We therefore used the population of England (56,536,000) rather than the whole UK population (67.0 million) for our calculations. This changes the current population coverage of CPRD Aurum from around 20% of the UK (reported in the March 2022 release notes) to around 25% of England.

Incidence

Due to the limitations in CPRD's feasibility tool, we were unable to remove people who already had Alzheimer's disease from the denominator for our incidence calculation. Therefore, the denominator is not strictly restricted to the population at risk. In addition, the values we have calculated represent the risk of Alzheimer's disease (or MCI) in one year, rather than the incidence, as we are unable to ascertain the amount of time people at risk at the start of the year remain at risk in that year. Furthermore, while the new cases identified were new cases in a given year, we could not restrict these new cases to those from the population at risk at the beginning of the year, meaning the new cases are not necessarily drawn from the denominator. It will include patients newly diagnosed with Alzheimer's in a given year who registered to a contributing practice mid-year or who's practice started contributing to CPRD mid-year.

Prevalence

Given that the number of practices contributing data changed each year, the population at risk differed in each of the 3 years included in our prevalent data. We therefore used the midpoint for the number of people at risk to calculate the prevalence.

Results

Alzheimer’s disease

Incidence

The number of new cases of Alzheimer's seen each year was relatively stable across 2013–2018, with an expected drop-off in years where COVID-19 substantially affected NHS services. COVID-19 affected the first few months of 2020, which appear in the 2019 data due to an April to March selection period, and the 2020 and 2021 data.

These figures equate to a risk of Alzheimer’s in non-COVID years of 13.67 to 15.76 cases per 10,000 people, or 77,270 to 89,112 cases per year in England.

Table: new cases of Alzheimer's disease per year

Start date	Number of new cases	Risk per 10,000 people	Population level estimates
01/04/2013	17,155	13.85	78,289
01/04/2014	19,460	15.76	89,112
01/04/2015	18,978	15.07	85,222
01/04/2016	18,658	14.53	82,138
01/04/2017	18,253	13.91	78,640
01/04/2018	18,312	13.67	77,270
01/04/2019	16,651	12.17	68,799
01/04/2020	9,957	7.12	40,280
01/04/2021	10,250	7.25	40,991

Mild cognitive impairment

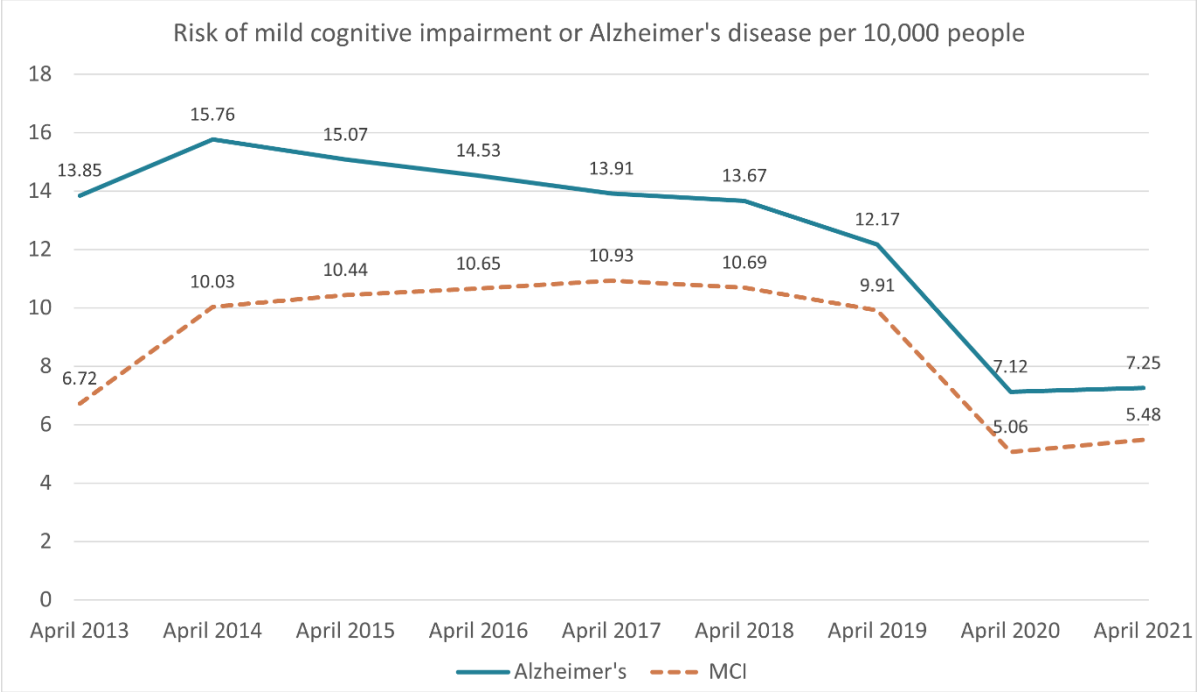
When we queried the mild cognitive impairment codes, the pattern was similar to cases of Alzheimer's disease, although values were lower at all time points. The overall reduction in COVID-19 years was also replicated (see table: new cases of mild cognitive impairment per year and figure: risk of mild cognitive impairment or Alzheimer's disease).

These results are consistent with our initial concerns that people with mild cognitive impairment may not present to health services in this early phase. This is particularly notable because these figures represent all causes of mild cognitive impairment, not just Alzheimer's disease.

Table: new cases of mild cognitive impairment per year

Start date	Number of new cases	Risk per 10,000 people	Population level estimates
01/04/2013	8,325	6.72	37,992
01/04/2014	12,389	10.03	56,732
01/04/2015	13,143	10.44	59,020
01/04/2016	13,683	10.65	60,237
01/04/2017	14,345	10.93	61,803
01/04/2018	14,325	10.69	60,447
01/04/2019	13,559	9.91	56,023
01/04/2020	7,076	5.06	28,625
01/04/2021	7,752	5.48	31,001

Figure: risk of mild cognitive impairment or Alzheimer's disease



Mild cognitive impairment and Alzheimer's disease

Mild cognitive impairment diagnoses

In 2016–19, a total of 10,591 people had both a mild cognitive impairment code and an Alzheimer's disease code. This equated to a prevalence of 7.97 cases per 10,000 population and a population level of 45,101 cases in England.

In the COVID-19 affected period, 2019–22, a total of 7,466 people had codes for both mild cognitive impairment and Alzheimer's disease, which equates to 5.32 cases per 10,000 and a population level of 30,105 cases.

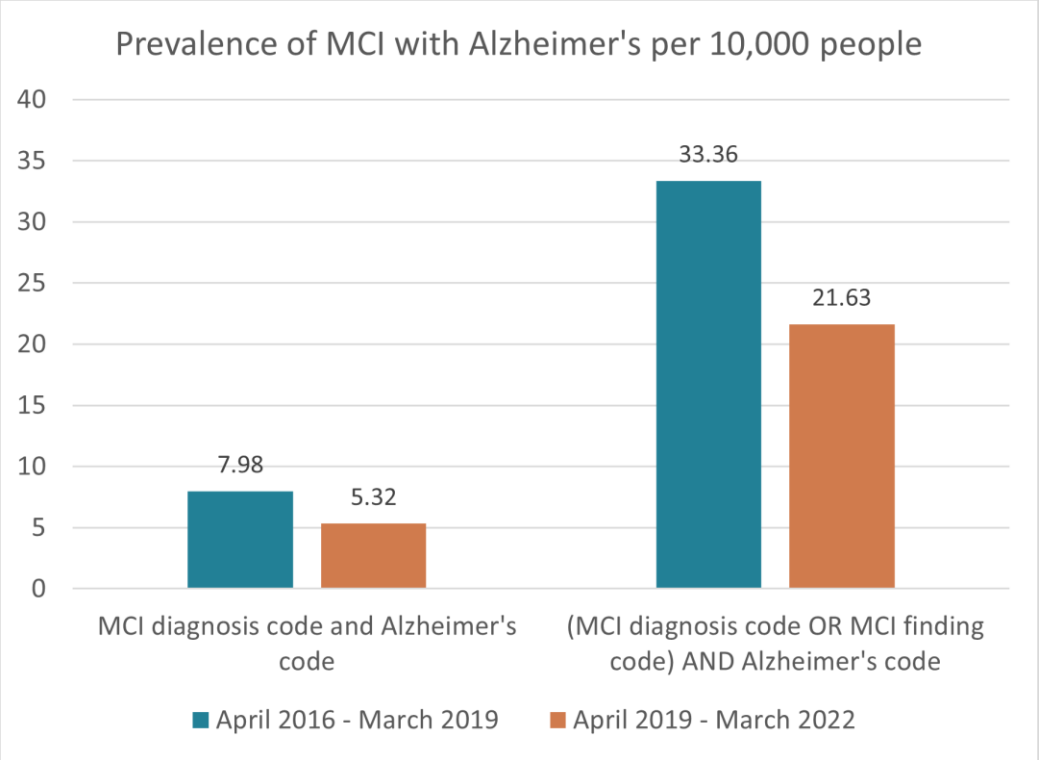
Cognitive impairment clinical findings

In 2016–19, a total of 44,287 people had an Alzheimer's disease code and either a mild cognitive impairment diagnosis code or a cognitive impairment clinical finding code. This equated to a prevalence of 33.36 cases per 10,000 population and a population level of 188,591 cases in England.

In the COVID-19 affected period of 2019–22, a total of 30,329 people had an Alzheimer's disease code and either a mild cognitive impairment diagnosis

code or a cognitive impairment clinical finding code, which equates to 21.63 cases per 10,000 and a population level of 122,295 cases.

Figure: Prevalence of people with a diagnosis of Alzheimer's disease and cognitive impairment codes in a 3-year period



Interpretation

We used several strategies to identify people with mild cognitive impairment or Alzheimer's disease in UK general practice. Overall, figures for Alzheimer's disease appear to be reliable, whereas mild cognitive impairment does not appear to be captured well in current clinical practice.

Alzheimer's disease

The results for number of people with Alzheimer's disease are likely to be reasonably accurate because the diagnostic codes are specific and unlikely to have a high rate of misclassification. However, the absence of consistent stage information remains a problem. The extrapolation to the population of England may be overly simplistic, which could bias the results.

We know of regional variations both in dementia diagnoses (Alzheimer's Society 2021) and CPRD coverage (Wolf et al. 2019). Further work may be warranted to determine how the areas of CPRD coverage map against areas of higher or lower rates of dementia diagnosis, allowing for more robust estimates at the national level.

We know that the proportion of over 65s in CPRD (17.3% of participants in September 2018; CPRD Aurum data resource profile) broadly aligns with the overall population (18.5% in January 2021; ONS overview of the UK population: January 2021). Therefore, the data should adequately capture people most at risk of Alzheimer's due to their age. However, we did not consider the effects of an ageing population on the number of people likely to have Alzheimer's disease. The number of people eligible for treatment is likely to increase over time as the population ages.

The NHS may be currently catching up on diagnoses of Alzheimer's disease that were delayed by COVID-19. This may affect the overall incidence seen in 2022 and 2023. However, it would not necessarily translate into an increase in the number of people eligible for new treatments. People may be being diagnosed later than if COVID-19 was not a factor, and thus may have disease that is too advanced for these treatments.

Mild cognitive impairment

Mild cognitive impairment appears to be under-recorded, possibly driven by people not presenting to general practice at this early stage. This means that we cannot draw any useful conclusions on the size of the population with mild cognitive impairment in the UK. In the current context of Alzheimer's disease as an untreatable progressive disorder it is understandable that people may not see any benefit in early diagnosis. There is a possibility that the introduction of new treatments increases the number of people presenting with mild symptoms. It may be worthwhile monitoring the effects on primary care resources after the launch of these new treatments.

Mild Alzheimer's disease

We used diagnosis of mild cognitive impairment and clinical findings of cognitive impairment and a diagnosis of Alzheimer's disease as a proxy for mild Alzheimer's disease.

The values for diagnosis of both Alzheimer's disease and mild cognitive impairment (around 10,600 cases within 3 years) are likely to be an underestimate because of the under-reporting of mild cognitive impairment. On the other hand, the value for people with a diagnosis of Alzheimer's disease and mild cognitive impairment or clinical findings of cognitive impairment may be more representative (around 44,300 people within 3 years). Nevertheless, the cognitive impairment clinical findings are not definitively linked with mild illness.

A final caveat on the approach to linking cognitive impairment with Alzheimer's disease is that in the feasibility approach we could only detect the presence of both the Alzheimer's concepts and the cognitive impairment concepts between set dates. This approach would exclude people with both diagnoses, within 3 years, where the dates of each diagnosis fell into a different 3-year bucket. In a full epidemiological study, we could better link these concepts as occurring within 3 years in each individual person.

The number of Alzheimer's disease diagnoses, that is, around 80,000 new cases per year, may thus be the best estimate of the population eligible for screening for beta-amyloid, even without a recorded stage of disease at diagnosis. This relies on the assumption that, in a perfect system, it is possible to detect all cases of Alzheimer's disease at the mild cognitive impairment stage. In reality, however, many of these patients will be ineligible for treatment due to comorbidities, being on contraindicated medication or treatment and functional status. Further work to understand the comorbidities in people with Alzheimer's would help to refine these values.

Triangulation with other estimates

Our estimated screening population of around 80,000 initially appears to be high when compared with other estimates. The decision support unit

estimated a prevalence of mild dementia of around 73,000 people. If our estimated annual rate of 80,000 cases and a duration of mild disease of 3 years would potentially give a prevalence of 240,000 cases. However, under the assumption that we could identify cases at mild cognitive impairment stage, then this figure correlated closely to the estimate for the total population of mild cognitive impairment and mild Alzheimer's of around 283,400. It also correlates well with the estimate of 286,000 people with mild Alzheimer's disease produced by Alzheimer's research UK (Email correspondence, Alzheimer's research UK, July 2023).

Insights for future epidemiological studies

Further work on a robust epidemiological study is warranted. Specific aspects of work that could deliver more robust results include:

- Checking whether patient data comes from areas of high or low dementia diagnosis and accounting for this in population estimates
- Understanding how the ageing population might affect diagnoses of Alzheimer's disease in the medium and long term.
- Establishing a valid proxy measure for mild cognitive impairment and mild Alzheimer's disease
- Better understanding of the links between diagnosis of mild cognitive impairment and subsequent diagnosis of Alzheimer's disease.
- Good characterisation of the population with Alzheimer's disease including the rates of comorbidities that would make new treatments unsuitable for individual patients.

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Robert Willans, Technical Adviser in NICE's Data and analytics team oversaw the discussions and decisions made during the project.

Richard Perry, Consultant Neurologist at Imperial College Healthcare NHS Trust, reviewed the code lists.

NICE's HTA lab team oversaw the work. Please see their full report for details of responsibilities.

Code lists

Table: Alzheimer’s disease diagnosis

Term	CPRD Aurum MedCodeId	SNOMED CT SCTID
Alzheimer's disease	45046017	26929004
[X]Dementia in Alzheimer's disease	295668011	26929004
[X]Dementia in Alzheimer's dis, atypical or mixed type	295671015	26929004
Dementia in Alzheimer's disease with late onset	376541000006112	416975007
[X]Alzheimer's dementia unspec	363021000006113	26929004
FH: Alzheimer's disease	1488581017	394877006
[X]Senile dementia,Alzheimer's type	425901000006116	416975007
[X]Dementia in Alzheimer's disease, unspecified	295672010	26929004
Alzheimer's disease with early onset	499946014	416780008
Alzheimer's disease with late onset	500317011	416975007
[D] Dementia in Alzheimer's disease	914951000006114	914951000006105
Dementia in Alzheimer's disease with early onset	376531000006119	416780008
Dementia in Alzheimer's dis, atypical or mixed type, other mixed symptoms	1972341000006111	1972341000006107
Dementia in Alzheimer's disease, unspecified, other mixed symptoms	1972471000006111	1972471000006107
Dementia in Alzheimer's dis, atypical or mixed type, without additional symptoms	1972231000006114	1972231000006105
Alzheimer dementia	2931251000006113	26929004
Primary degenerative dementia of the Alzheimer type, senile onset	6900181000006114	416975007
[X]Presenile dementia,Alzheimer's type	423351000006115	416780008
[RFC] Alzheimer's disease	905791000006115	905791000006104
[X]Other Alzheimer's disease	299325013	26929004

Dementia in Alzheimer's disease with late onset, other mixed symptoms	1972211000006115	1972211000006104
Primary degenerative dementia of the Alzheimer type, presenile onset	6897211000006117	416780008
[X]Alzheimer's disease type 1	363031000006111	416975007
[X]Primary degen dementia of Alzheimer's type, senile onset	423381000006111	416975007
Dementia in Alzheimer's disease with early onset, other mixed symptoms	1972141000006113	1972141000006109
Alzheimer disease	2931241000006111	26929004
Dementia in Alzheimer's disease - type 2	6897271000006114	416780008
MVAD - Mixed vascular Alzheimer dementia	12370651000006112	79341000119107

Table: Mild cognitive impairment diagnosis

Term	CPRD Aurum MedCodeId	SNOMED CT SCTID
Cognitive decline	1491798012	386806002
Mild cognitive disorder	215831000000117	386805003
Mild cognitive impairment	2288201000000116	386805003
Cognitive impairment	1491795010	386806002
GDS level 3 - mild cognitive decline	2159231011	407631005
GDS level 2 - very mild cognitive decline	2159230012	407630006
Mild cognitive impairment review	2638111000000116	1047041000000108
Dementia stage at diagnosis - early (mild)	1949631000006115	1949631000006104
Referral to dementia early intervention service	1933001000006115	1933001000006104

Table: Cognitive impairment clinical finding

Term	CPRD Aurum MedCodeId	SNOMED CT SCTID
[X]Other amnesia	318024017	48167000
Memory loss - amnesia	495013011	48167000
Amnesia symptom	479241000006114	48167000
Amnesia	711391000006112	48167000
Memory loss	3279341000006111	48167000
Loss of memory	3279381000006117	48167000
Amnesia for recent events	3179831000006112	42176003
Loss of memory for recent events	3179841000006119	42176003
Amnestic mild cognitive disorder	13935251000006116	836301008
aMCI - amnestic mild cognitive impairment	13935261000006119	836301008
Cognitive disorder	7274731000006114	443265004
Disorientated in place	3677971000006113	72440003
Disorientated in time	479781013	19657006
Forgetful	497290018	55533009
Forgets recent activities	5246211000006118	247595006
Forgets what has just done	5246221000006114	247596007
Forgets what has just heard	5246261000006115	247600002
Forgets what has just said	5246231000006112	247597003
Getting lost	5247121000006118	247664009
GDS level 2 - very mild cognitive decline	2159230012	407630006
GDS level 3 - mild cognitive decline	2159231011	407631005
Has delayed recall	5681441000006118	283902008
Cognitive impairment	1491795010	386806002
Cognitive decline	1491798012	386806002
Impaired cognition	404241000006118	386806002
Impaired cognition	1807641000006115	386806002
Cognitive disturbance	6462081000006114	386806002
Cognitive dysfunction	6462091000006112	386806002
Cognitive deficit	6462111000006115	386806002
Memory deficit	1222481019	386807006

Memory impairment	1480927011	386807006
Memory disturbance	711371000006111	386807006
Memory dysfunction	6462141000006116	386807006
Impaired memory	6462151000006119	386807006
Memory problem	6462171000006112	386807006
Poor memory	6462181000006110	386807006
Bad memory	6462191000006113	386807006
Disturbance of memory	6462201000006111	386807006
Memory lapses	4935551000006118	225038006
Memory loss care assessment	6768901000006114	408902006
Memory: address recall unsuccessful	711421000006116	165308007
Memory: important event not kn	257037016	165298000
Memory: important event not known	14068591000006116	165298000
Memory: present month not knwn	257033017	165295002
Memory: present month not known	14068581000006119	165295002
Memory: present place not known	710751000006111	165286005
Memory: present time not known	257017015	165283002
Memory: present year not known	257025018	165289003
Mild cognitive disorder	215831000000117	386805003
Mild cognitive impairment	2288201000000116	386805003
Mild memory disturbance	295525018	192071009
Minimal cognitive impairment	4178371000006110	110352000
Minor memory lapses	4935541000006115	225037001
Short-term memory loss	369704019	247592009
Poor short-term memory	5246161000006110	247592009
Short term memory loss	5246181000006117	247592009
Referral to memory assessment service	8271251000006117	823961000000102
Referral to memory clinic	2534215016	415276009
Retrograde amnesia	317084016	51921000
Spatial disorientation	4203781000006111	112077003
Unable to recall random address at five minutes	5698651000006114	285208000