Appendix D

Estimates of the size of the English eligible population in for amyloid targeting therapies in Alzheimer's Disease

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is based at the University of Sheffield with members at the Universities of York, Bristol, Leicester, Warwick and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information: https://www.sheffield.ac.uk/nice-dsu

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EXECUTIVE SUMMARY

A series of potentially disease modifying therapies for Alzheimer's Disease (AD) are close to obtaining marketing authorisation and subsequent appraisal by NICE. Lecanemab is one such treatment where the NICE appraisal process has started. The key Phase 3 clinical trial of lecanemab was conducted in patients at an early stage of AD with either mild cognitive impairment (MCI) due to AD or mild dementia due to AD. The size of the patient population at this early stage of AD may be substantial. In addition, eligibility for treatment in the trial required evidence of amyloid positivity by positron-emission Tomography (PET) or cerebrospinal fluid (CSF) biomarkers. Neither of these tests are widely used in current, NHS standard practice. They are invasive and costly procedures. This report provides estimates of the size of the populations in in England that may be eligible amyloid testing and the proportion of those that may be eligible for treatment.

We use an approach described in two publications[7,10] to make these estimates. We use the same sources of evidence to produce central estimates and upper and lower scenarios drawing on other relevant sources.

The central estimates are that there are around 210k people with MCI AD and around 100k of those would be expected to be amyloid positive. There are approximately 73k people with mild dementia due to AD and 62k would be expected to be amyloid positive. However, these estimates are subject to significant uncertainty because the majority of the evidence, particularly for the prevalence of MCI, relates to people aged over 65years. The population of England is doubled if those aged 50 – 65 years are included. Evidence sources are sometimes from studies set in other countries. Even where systematic reviews are used, these can contain also contain studies of less relevance to current, NHS practice.

In addition, these estimates do not reflect the full populations that would either need to be screened or treated. Many other factors would also be used to determine whether patients would be candidates for disease modifying treatments such as the presence of comorbidities, the willingness to undergo either PET scans or lumbar puncture, as well as the willingness to take these therapies. These other factors would be assessed before providing invasive and costly tests

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ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's Disease
ARIC	Atherosclerosis Risk in Communities Study
CDR	Clinical Dementia Rating
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CSF	Cerebrospinal fluid
EMA	European Medicines Agency
EU	European Union
ICER	Institute for Clinical and Economic Review
IDEAS	Imaging Dementia—Evidence for Amyloid Scanning study
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
NIA-AA	National Institute of Aging–Alzheimer's Association
OHID	Office for Health Inequalities and Disparities
ONS	Office for National Statistics
PET	Positron-emission Tomography

1. Introduction

A series of potentially disease modifying treatments for Alzheimer's Disease (AD) are nearing the point of obtaining marketing authorisation and appraisal for use in the NHS by NICE.

Several of these new treatments are based on the belief that amyloid protein removal from the build-up in the brain, slows the progression of disease. Lecanemab (marketed as Leqembi, Eisai Co Ltd) is one such anti-amyloid agent that is scheduled for NICE evaluation, with the suggested remit and draft scope available on the NICE website from March 2023.

Two issues, *inter alia*, are likely to raise significant challenges for health systems for the delivery of agents such as lecanemab, as well as impacting the overall budget impact and/or cost-effectiveness estimates. These are a) the size of the eligible patient population and b) the number of people that may need to be screened in order to establish eligibility.

The key Phase 3 clinical trial of lecanemab (Clarity AD), described in more detail below, was conducted in patients at an early stage of AD with either mild cognitive impairment (MCI) due to AD or mild dementia due to AD. It is estimated that the average duration of MCI due to AD lasts between 3 and 7 years, and mild dementia between 2 and 4 years[1]. The size of the patient population at this early stage of AD may be substantial.

In addition, eligibility for treatment in the trial required evidence of amyloid positivity by positron-emission Tomography (PET) or cerebrospinal fluid (CSF) biomarkers. Neither of these tests are widely used in current, NHS standard practice. They require invasive, costly procedures. The NICE Clinical Guideline for dementia (NG97)[2] states that these procedures should only be used in those circumstances where the diagnosis is uncertain and the use of these further tests, beyond the use of validated criteria guiding clinical judgement, would help to diagnose a dementia subtype and this would change management.

The aim of this report is to assess the size of the eligible patient population (the potential "treatment population") and the number of screens that would potentially be required (the "screening population") were lecanemab to be approved, in England.

Note, there are numerous other reasons why patients may be ineligible for lecanemab (or other AD agents) that would further reduce the size of the treatment population. It is envisaged that this information will be of potential relevance to appraisals of other similar products (and other aspects of planning for the health system).

2. Clinical trial populations

2.1 Lecanemab

Clarity AD[3] was an 18 month treatment, placebo-controlled trial of people with early Alzheimer's disease which randomised eligible participants aged 50 to 90 years to receive either lecanemab or placebo. The study was conducted in approximately 200 sites in North America, Europe, Asia-Pacific, and China. Eligible patients had either mild cognitive impairment due to AD, or mild AD dementia on the basis of National Institute on Aging-Alzheimer's Association criteria.

For those diagnosed as having MCI due to AD, participants had to:

1. Meet the National Institute of Aging–Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD–intermediate likelihood.
2. Have a global Clinical Dementia Rating (CDR) score of 0.5 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline.
3. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before screening; must be corroborated by an informant.

For those with mild AD dementia, participants had to:

1. Meet the NIA-AA core clinical criteria for probable AD dementia.
2. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline.

The NIA-AA criteria are intended to define the AD spectrum in terms of biomarkers and distinguish AD from non-AD causes of cognitive impairment. MCI is defined as the symptomatic, pre-dementia phase of AD. Mild changes in memory and thinking

are noticeable and can be measured on mental status tests but do not disrupt a person's everyday life. MCI may be caused by factors other than AD. The NIA-AA guideline for use in the research setting has four levels of certainty for ruling out these other causes and arriving at a diagnosis of MCI due to AD[4], depending on the presence and nature of biomarker findings.

In addition, participants were required to have amyloid positivity determined either by PET scan or CSF measurement of amyloid-beta (Aβ) protofibrils.

Limited details are provided on screening failures in the published information for Clarity AD. 1795/5967 (30%) entered the treatment trial with 4172 (70%) not proceeding past the screening stage[3]. The majority of these screening failures were due to "not meeting the inclusion criteria or met exclusion criteria" (3555/5967 = 59.6%). This category is broader than simply those that were excluded because they were not amyloid positive at screening. In addition, 201 (3.4%) withdrew consent, which may have been related to the requirement to undergo screening.

2.2 Aducanumab

Aducanumab (Aduhelm, Biogen) for treating MCI and mild dementia caused by AD was scheduled for a NICE appraisal (ID3763) but this was suspended following the decision of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to adopt a negative opinion, recommending the refusal of the marketing authorisation for aducanumab in December 2021.

There are two phase 3 trials of aducanumab, EMERGE and ENGAGE which were identically designed[5]. Both included patients aged 50 to 85 years who met clinical criteria for MCI due to AD or mild AD dementia, with amyloid pathology confirmed by visual assessment of amyloid positron emission tomography (PET; 18F-florbetapir, 18F-flutemetamol, or 18F-florbetaben).

EMERGE randomised 1643 participants (to either high dose aducanumab, low dose aducanumab or placebo) that had MCI due to AD or mild AD defined as:

- A Clinical Dementia Rating (CDR)-Global Score of 0.5.
- Objective evidence of cognitive impairment at screening

- A Mini Mental State Examination (MMSE) score between 24 and 30 (inclusive)

ENGAGE randomised 1647 participants.

However, the study publications do not report how many were screened and found to be amyloid positive.

2.3 Donanemab

TRAILBLAZER-ALZ 2 was a phase 3 clinical trial of donanemab for early symptomatic AD, published 17th July 2023[6]. 8240 adults with early symptomatic AD were assessed for eligibility, with 1736 participants aged 60-85 years with MCI or mild dementia due to AD subsequently randomised to donanemab or placebo. Sims et al provide full details of the participant flow leading to randomisation[6].

They report 18 different categories for exclusion of 6504 participants. Of these, just 1601 were excluded due to low amyloid pathology (19.4% of the starting population) with large proportions of participants found not to meet other exclusion criteria. In this study, participants were also required to have presence of tau pathology assessed by PET scan and a similarly large proportion of the population were excluded on the basis of low tau pathology (1631, 19.8%). It is not clear how many of these patients may also have been excluded on the basis of low amyloid pathology.

3. Estimates of the size of the Screening and treatment populations

Potashman et al (2020)[7] describe a “funnel based approach” to estimating the prevalence of those with either MCI or mild dementia due to AD and subsequently positive for amyloid after screening. They used this approach to estimate population sizes for five European counties combined (France, Germany, Italy, Spain and the UK). Figure 1 illustrates the steps involved in the analysis. This approach was produced by employees of Biogen and components of these estimates can also be found in the US Institute for Clinical and Economic Review (ICER) budget impact analyses which form part of their assessment reports both for aducanumab[8] and

lecanemab[9]. It is also an approach that has been applied to the US population, with the methods explained in greater detail in an associated publication[10].

Starting with the relevant overall population the first step requires estimates of the prevalence of MCI or dementia (of any severity at this point) in that population. This is then refined to estimate the number of people that present to a healthcare provider (step 2), that are suspected of AD based on clinical symptoms (step 3), and the proportion with amyloid beta confirmed (step 4).

These estimates use different parameters for the MCI and mild dementia subpopulations. For the dementia subpopulation it is at stage 3 in Figure 1 where both the clinical confirmation of AD and the proportion of AD that is mild dementia is calculated.

We use this approach to provide estimates for the population of England. Estimates presented reflect both the sources used by Potashman et al and other sources/values, where considered appropriate. Each step of the calculation is reported in Table 1 and Figures 2 and 3. We also report each of these steps when applied to the highest and lowest estimates within the ranges we identified (see Table 2 and Table 3).

Figure 1: Funnel approach from Potashman et al

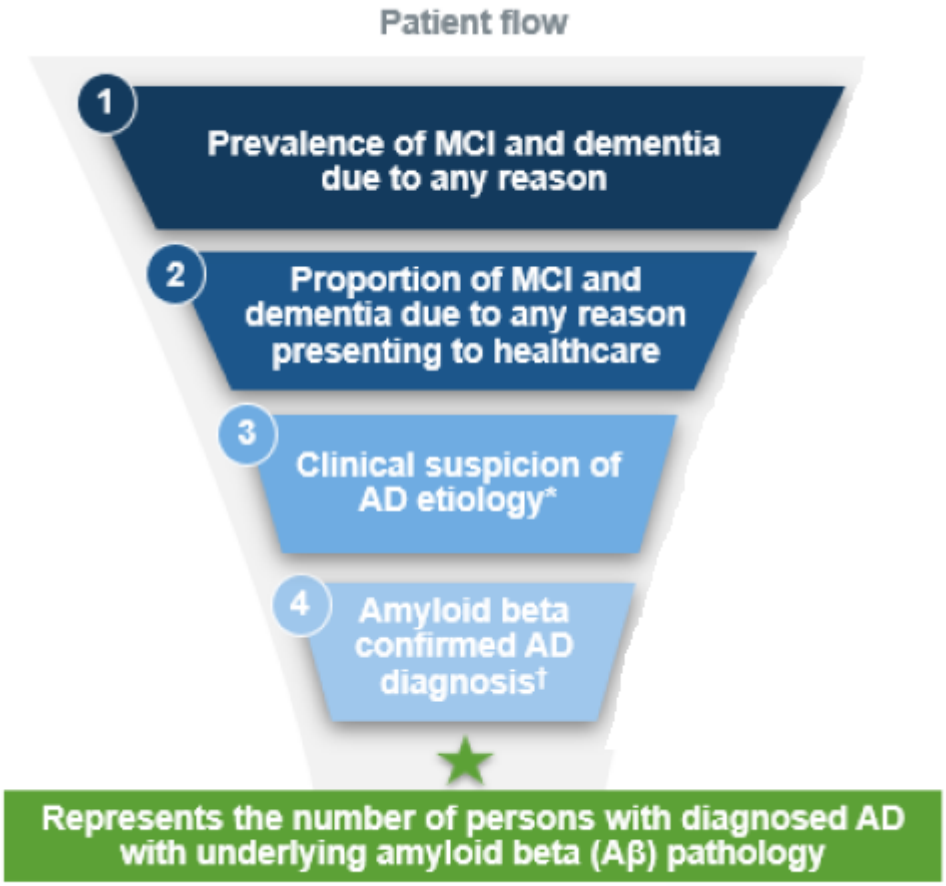

Table 1: Estimates of the size of the treatment and screening populations using the Potashman et al stages for England

Stage	Population	MCI		Dementia		Total	
		N	%	N	%	N	%
		20,079,568		20,079,568		20,079,568	
1		2,108,355	10.5%	763,024	3.8%	2,871,378	14.3%
2		280,411	1.4%	292,238	1.5%	572,649	2.9%
3	Screening	210,308	1.0%	73,091	0.4%	283,399	1.4%
4	Treatment	99,476	0.5%	61,835	0.3%	161,311	0.8%

Figure 2: Illustration of estimates for each stage of calculations for the MCI population of England.

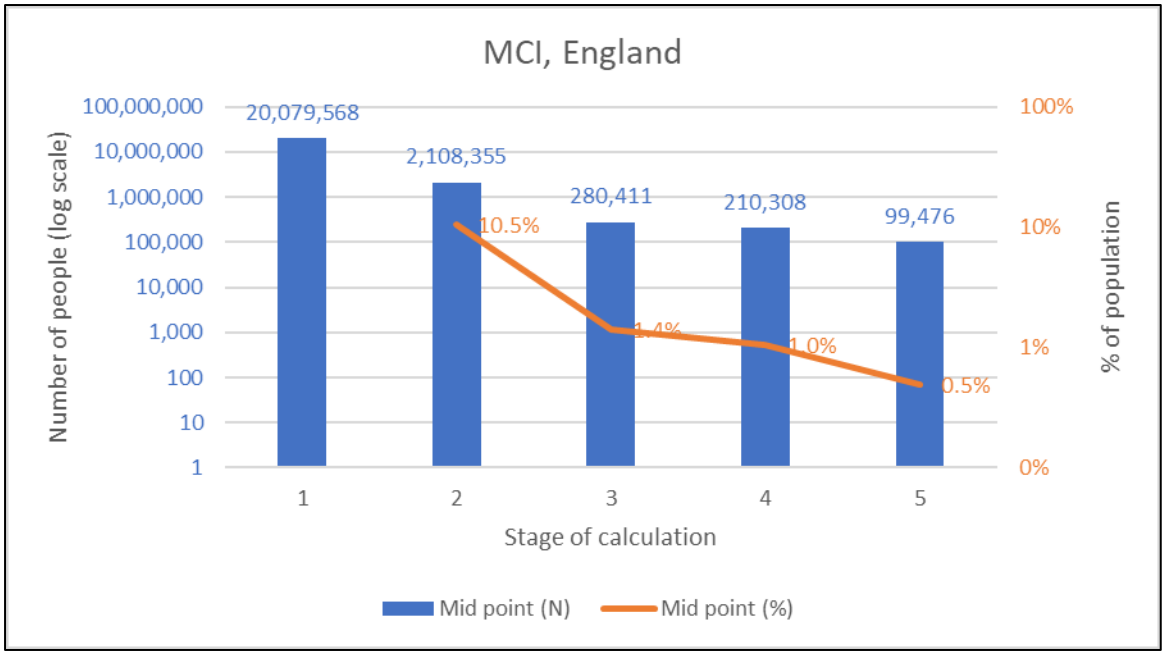

Figure 3: Illustration of estimates for each stage of calculations for the mild dementia population of England.

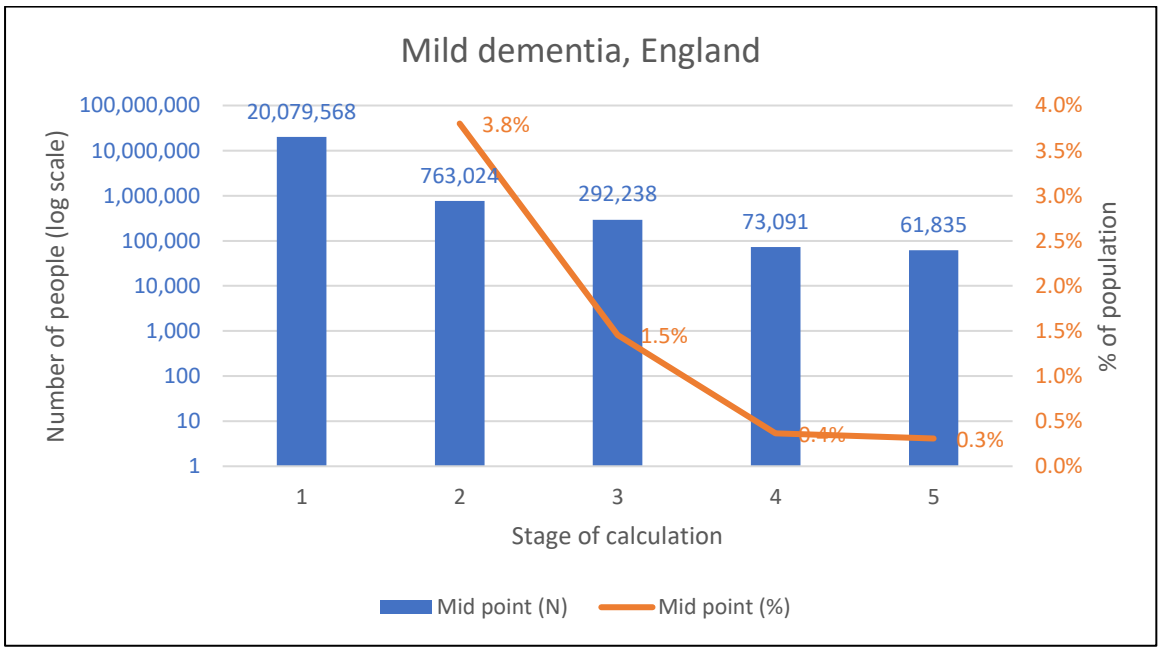

Table 2: Upper and lower ranges of estimates for MCI

Stage	Upper		Source	Lower		
	20,079,568		ONS England 65+	10,468,153		ONS England 65+
1	5,401,404	26.9%	26.9% (Upper CI Peterson et al broadly defined population)	502,471	4.8%	4.8% (Lower CI Peterson et al narrowly defined population)
2	718,387	3.6%	13.3% (Anstey et al.)	66,829	0.6%	13.3% (Anstey et al.)
3	538,790	2.7%	75% (Knopman et al)	50,122	0.5%	75% (Knopman et al)
4	297,951	1.5%	55.3% (Rabonivici et al)	23,707	0.2%	47.3% (as Potashman et al)

Table 3: Upper and lower ranges of estimates for mild dementia

Stage	Upper		Source	Lower		
	20,079,568	0.0%	ONS England 65+	10,468,153	0.0%	ONS England 65+
1	1,353,363	6.7%	6.74% (NHS England)	397,790	3.8%	3.8% (AD Europe)
2	518,338	2.6%	38.3% (Lang et a.)l	152,353	1.5%	38.3% (Lang et al.)
3	169,186	0.8%	32.6% (68% Tognoni et al x 48% Herbert et al)	38,105	0.4%	25% (58% Tognoni et al x 43% Herbert et al)
4	143,131	0.7%	84.6% (Herbert et al)	26,711	0.3%	70% (Rabonivici et al)

3.1 Population for England

The Office for National Statistics (ONS) population estimates for England for mid-2021[11] for those aged 50-84 years (following the calculations reported in Potashman et al and in line with the trials for aducanumab) is 20.1m. Note that the inclusion criteria for the Clarity AD trial stipulated participants must be in the age range of 50-90 years[3].

For the population aged 65-90 years, the size of the population of England is 10.5m[11]. Given the source of some of the subsequent estimates, this may be a relevant population to consider.

3.2 Prevalence of MCI or dementia (for any reason)

MCI

Potashman et al refer to an estimate of 11% for the prevalence of MCI in the population of people aged 50-84years, citing Peterson et al (2018)[12]. Peterson is also the source paper used for this parameter in a Rand Research Report[13].

Peterson et al (2018) is a report of the update of the American Academy of Neurology Guideline on MCI which includes a systematic review of the prevalence of MCI. Peterson et al report prevalence by 5-year age bands as shown in Table 2 below. The extent of rising prevalence with age is evident. The paper did not report a figure of 11% as the estimate of prevalence of MCI in the population for those aged 50yrs and over (most evidence pertains to populations over 65 years and the minimum age range was 55 years and over). However, in the full guideline[14], it is reported that a meta-analysis of all Class I studies (n=22) with individuals aged 65 years and older resulted in a prevalence of 16.62% (95% CI 11.59%–26.9%, I2 23.54) verses those studies that used a narrow definition of MCI study prevalence of 10.5% (95% CI 4.8%–21.5%, I2 20.4).

We apply the figure of 10.5% to the population aged 50-84 in our replication of the Potashman et al calculations for England. This gives an estimate of **2.1m people** with MCI.

Given that there is little evidence for the rate of MCI in those aged under 65 years, an alternative estimate restricts the size of the starting population to those aged 65 years and over. This gives an estimate of **1.1m people** with MCI.

A 3rd alternative is to use the age specific estimates reported in Table 2 for those aged between 60 and 84 years. These give an estimate of **1.4m people** with MCI. It should be noted that this 3rd option is based on the results from studies using a broader rather than narrower definition of MCI, highlighting that there is variation caused by both the relevant starting population and the differing potential definitions of MCI used across studies.

We also calculate estimates for the upper and lower range of estimates using a) the upper 95% Confidence Interval (CI) for MCI broadly defined (29.9%) and b) the lower bound of the 95% CI for MCI narrowly defined (4.8%). Applying these figures to the broader age group gives an upper estimate of **5.4m**, and when using the narrower age group for England a lower estimate of **0.5m**.

Table 4: MCI guideline meta-analysis results: Prevalence of MCI by age group (random-effects model). Reproduced from Peterson et al[14]

Age group	Prevalence
60–64 y	6.7% (95% CI 3.4%–12.7%) I_2 = 11.0
65–69 y	8.4% (95% CI 5.2%–13.4%) I_2 = 0
70–74 y	10.1% (95% CI 7.5%–13.5%) I_2 = 5.2
75–79 y	14.8% (95% CI 10.1%–21.1%) I_2 = 60.7
80–84 y	25.2% (95% CI 16.5%–36.5%) I_2 = 0
60+ y	All studies 15.8% (95% CI 11.8%–20.9%) I_2= 0
65+y	All studies 16.6% (95% CI 11.5%–23.5%) I_2 = 13.3
75+y	All studies 19.4% (95% CI 15.7%–23.7%) I_2 = 29.7
80+y	All studies 28.6% (95% CI 20.5%–38.4%) I_2 = 27.5
85+y	All studies 37.6% (95% CI 28.1%–48.0%) I_2 = 24.8

Abbreviation: MCI = mild cognitive impairment.

Mild Dementia

Potashman et al estimate that 3.8% of the population aged 50-84 years have dementia (of any severity and not solely due to AD), drawing estimates from Alzheimer Europe Annual Reports for 2019[15]. This is a study that uses estimates of prevalence from a systematic review of the literature and applies these to the populations of European countries.

For the purposes of comparison, the Office for Health Inequalities and Disparities (OHID)[16] estimates of the prevalence of AD and dementia for England was 4.0% (CI 4.0 to 4.0) of the over 65 (note the slightly different age categories here) patient population in December 2020.

NHS England[17] figures for May 2023 suggest that in the over 65s, there are 705,655 people with dementia (with and without a recorded diagnosis). That is 6.4% of the population over 65 years registered to a GP in England at May 2023. It is 6.74% of the 2021 estimated population 65+ from ONS.

The estimates using the preferred Potashman et al figures for England is **763k people** with dementia.

Applying the same proportion to the smaller, over 65 population, would lead to estimates of **398k people**.

Using the highest figures from NHS England of 6.4%, and applied to the entire 50-84 year old population, would result in an estimate of **1.35m people**.

3.3 Proportion that present to the Healthcare system

MCI

The Potashmann et al estimate is 13.3% of those with MCI. This comes from Anstey et al[18], who report the results of a study which followed a community-based cohort of 60-64 year olds, originally recruited in 1999, for 8 years and assessed them for MCI every 4 years (n=2551). Participants were recruited from the electoral rolls of two regions of Australia.

Applying this figure to the previous stages leads to estimates of **280k people** with MCI presenting to healthcare (scenario consistent with other values used in Potashman et al), with **718k** (highest estimate from the previous stage) to **67k** (lowest) (see Table 2).

Mild Dementia

Lang et al[19] conducted a systematic review and meta-analysis of 23 studies on the prevalence of undetected dementia in the community. They report a figure for the rate of undetected dementia as 61.7% (95% CI 55.0% to 68.0%). This is consistent with the figure quoted in Potashman et al. (100% - 61.7%). It should be recognised that this review covers studies relating to worldwide health systems, many are quite dated (spanning 1988 to 2015) with practice likely to have improved, and relates to dementia overall, not MCI or mild dementia due to AD (this adjustment takes place in the next

stage). The rate of undetected dementia may not fully reflect the probability of presenting to healthcare.

Applying this figure to the previous stages of the calculation leads to an estimate of **292k people** with dementia presenting to healthcare in England. The higher and lower ranges of this estimate, based on the figures reported for the previous stages are **518k people** and **152k people** respectively.

3.4 The proportion clinically diagnosed with AD

MCI

Potashmann refer to Knopman et al[20] for the source of an estimate of 75% of those with MCI that present being clinically diagnosed with AD. This was based on a large dementia surveillance study (the Atherosclerosis Risk in Communities (ARIC) Study). This was a US study that recruited almost 16,000 individuals between 1987 – 89. In this paper, visits between 2011-13 from the surviving cohort for whom cognitive diagnoses could be ascertained (n=6471) are reported. 21% had MCI. Alzheimer's disease was the primary or secondary aetiology in 1021/1371 (75%) of MCI participants.

Applying this rate to the previous steps leads to estimates of **201k people** suitable for screening (**539k** and **50k** being the higher and lower estimates).

Mild Dementia

There are two separate estimates within this stage of the Potashman et al approach since the estimates to this point are based on dementia of all stages, not specifically mild dementia:

a) The proportion of dementia cases overall that have AD drawing on an Italian study by Tognoni et al[21]. 1600 participants aged over 65 years were screened for MCI or dementia from a single municipality of Tuscany, with 354 (22.1%) scoring below the cut-off value in the MMSE or the CDR. Potashman et al use a figure of 58.3%. An alternative figure in the study reports that 68% of subjects with dementia were clinically assessed as having AD (see page 68 of Tognoni et al).

b) The proportion of AD dementia cases that have mild dementia. Potashman cite a figure of 42.9% of AD cases being mild, referring to Hebert et al[22]. Hebert is a US study from 2003 that uses evidence from three neighbourhoods of Chicago and applies the findings to the US population. They report that "48% of prevalent cases of AD were classified as mild" (p. 1120).

   It is worth noting that Jonsson et al[23] use figures from the Global Burden of Disease Study 2019, which reports that 48% of all AD dementia is mild (uncertainty range 38% - 58%).
   The Tognoni et al study also reports relevant estimates that 35% of patients with dementia were graded mild, based on a CDR = 1 (see page 69).

Using the figures cited by Potashman et al lead to estimates of **73k people** with mild dementia diagnosed in England. Applying these same proportions to the lower range of estimates from the previous stage leads to an estimate of **38k people**.

Both of the estimates within this stage of the calculations are based on sources that also include slightly higher estimates. Applying these to the higher range from the previous stages leads to an upper estimate of **169k people**.

These are estimates of the potential population that may be considered for screening for amyloid positivity and subsequent treatment.

3.5 The proportion of cases testing positive for beta amyloid

MCI

Potashman et al report 47.3% of MCI patients overall test positive but the source for this estimate is unclear in the poster presentation. Differential rates by age are reported ranging from 28% in the 50-54 year old group to 67% in the 80-84 year old group.

Rabonivici et al (see below for details) report that 3817/6905 (55.3%) of patients with MCI had positive amyloid PET scans.

The estimates using the figures cited by Potashman et al are **99k people** testing positive with MCI due to AD. Using the same starting figure from the previous stages

but using the slightly higher estimates from Rabonivici et al leads to estimates of **116k people**.

The highest and lowest estimates are **298k** and **24k people** respectively.

Mild Dementia

The estimate reported by Potashman is 84.6% from the Herbert et al (2003) US study described above in the previous stage of calculations.

A more up to date study is Rabinovici et al (2019)[24] which suggests 70.1% of people with a clinical diagnosis of mild dementia due to AD will test positive for amyloid beta. This US study, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study, was a single-group, multisite longitudinal study that assessed the association between amyloid PET and subsequent changes in clinical management for Medicare beneficiaries with MCI or dementia. 16008 patients where AD was a diagnostic consideration were enrolled in 2016-2017 and all underwent PET scans. The focus of the study was to determine the extent to which changes in management occurred pre and post PET visits. Among 3154 patients with dementia, 70.1% had positive amyloid PET scan results. The figure refers to all categories of dementia, not specifically mild dementia. However, the median MMSE was 22 (IQR 18-25). 21-24 is considered mild and 10-20 as moderate dementia. In addition, it should be noted that patients had AD as a potential diagnosis in this study.

Applying the estimates proportion from Herbert to the previous estimates consistent with the Potashman et al approach results in an estimated **62K people** eligible with mild dementia due to AD that test positive for amyloid. That figure drops to **51k people** if the Rabinovici et al estimate is used. The higher and lower estimates are **143k** and **27k** respectively.

3.6 Total populations

Summing the totals across the MCI and mild dementia subpopulations leads to estimates of the potential population eligible for screening:

- **283k people** that either have MCI due to AD or mild dementia due to AD when estimates are made using the sources and figures cited by Potashman et al. That is 1.4% of the English population aged 50-84 years.
- Combining all higher estimates, where we identified alternative figures, in the same population age range for England leads to an estimate of 708k people. 3.4% of the population.
- Combining all lower estimates and using the English population aged 65 years and older leads to an estimate of 88k people. That is 0.8% of this smaller population.

And the potential number of those patients that would test amyloid positive after screening:

- **161k people** when using the sources and figures cited by Potashman et al. That is 0.8% of the English population aged 50-84 years.
- The highest estimates are **441k people** and the lowest **50k.**

A recently published paper by Jonsson et al[23] provide estimates of the size of the amyloid positive MCI and mild dementia due to AD populations. Their estimates for European Union (EU) countries are derived from prevalence figures reported by Gustavsson et al[25]. Gustavsson et al is a 2023 targeted literature review which focusses on meta analyses of systematic reviews published in the past 10 years. Prevalence figures for amyloid positive dementia (of all severities) are reported by age (from 60 years and above), sex and by Global Burden of Disease world region. For MCI, the figures are reported by age category. Jonsson et al further assume that 1/3 of potentially eligible MCI patients will present. For dementia, it is estimated that 48% of total AD dementia cases are mild AD dementia.

Using these same figures, and additionally assuming a 50:50 split between males and females in each age category, applied to the population for England aged 60 years and over yields estimates for the eligible treatment population (that is, amyloid positive) of **367k people** for MCI due to AD and **222k** for mild dementia due to AD, a total of **589k people**. These figures are higher than the estimates made using the methods and sources described above and occur because the prevalence figures from Gustavsson et al appear higher, though this is difficult to disentangle because

this approach merges prevalence of MCI or dementia, prevalence of AD, and prevalence of amyloid positive AD into a single set of estimates.

Jonsson et al report overall figures of 575k, 834k, 851k and 1.1m for Spain, France, Italy and Germany respectively.

4. Discussion

We have provided estimates of the size of the English population that may have MCI or mild dementia due to AD, using a stepwise approach proposed by Potashman et al. The approach uses different stages of estimation starting with the overall population and refining that based on prevalence of either MCI or dementia for any reason, the probability that patients present to healthcare, and that they are diagnosed with AD. A final step estimates the probability that this “screening” population subsequently tests positive for the presence of amyloid. The approach we have used draws on relevant evidence at each stage but it can be seen from the range of estimates provided that there is significant uncertainty about the size of both populations.

Largely, the evidence is drawn from published systematic reviews but we did not conduct exhaustive, systematic searches for alternative studies ourselves. There are several other limitations:

- Studies of the prevalence of MCI in the population are largely drawn from populations over 65 years. Therefore, there is significant uncertainty about how relevant estimates are if applied to younger populations, even though therapies such as lecanemab have been trialled in broader populations. The starting population is clearly a major source of uncertainty in terms of the total number of patients in England, because the population is doubled if those aged between 50 and 64 years are included.
- Some sources are from studies that may be less relevant for current NHS practice. For example, estimates of the proportion of patients that present to healthcare are notoriously difficult to estimate. For MCI, our estimate comes from an Australian study. For dementia, whilst based on a systematic review, the included studies span a range of countries, and many of those studies are

quite dated. For both reasons, the results may be less generalisable to current NHS practice.

- It is also unknown how behavioural change may alter any estimates here if disease modifying treatments were to become available.
- The figures from Rabonivici et al on the probability of testing positive for amyloid after a PET scan seem to be based on a high-quality study. Caution needs to be exercised in interpreting these figures either in comparison to those reported in the relevant clinical studies or their use in any subsequent appraisal. In particular, the starting populations may not be comparable if there are mixed population of MCI and mild dementia due to AD, or if the diagnosis is based on biomarkers rather than clinical assessment.
- We have referred to the “screening population”. This is used to refer to the population with MCI or mild dementia due to AD. However, in practice many other factors would also be used to determine whether patients would be candidates for disease modifying treatments such as the presence of comorbidities, the willingness to undergo either PET scans or lumbar puncture, as well as the willingness to take these therapies. The impact of some of these factors can be seen in the published lecanemab and donanemab trials. These other factors would be assessed before providing invasive and costly tests. However, even allowing for these processes, and taking into account the lower bound of the estimates of 88k people, it is clear that a substantial challenge will need to be addressed in order to provide these treatments to those that may be eligible.

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