NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of dementia: assessment, management and support for people living with dementia and their carers (NICE guideline NG97)

Review decision

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Contents

Surveillance decision

We will not update the NICE guideline on dementia. However, because this topic is important to our stakeholders, we will refer it to our new topic prioritisation board for consideration.

Reason for the exceptional review

NICE were contacted by the Department of Health and Social Care to consider mild cognitive impairment (MCI) in the early prodromal phases of dementia in relation to the dementia strategy. NICE already has a guideline on dementia (NICE guideline NG97), which covers the diagnosis and management of dementia, but the scope currently excludes people with MCI except where they are already suspected of, or have a confirmed diagnosis of, dementia. NICE has also produced a guideline on dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset, which covers a range of strategies to promote a healthy lifestyle that reduce risk of dementia, disability and frailty, but does not cover adults with any type of dementia or pre-existing cognitive impairments. As such, NICE decided that an exceptional review of NICE guideline NG97 would be appropriate to consider if the guideline scope should be expanded to include MCI in the early prodromal phase of dementia.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the guideline in 2018.
- Feedback from topic experts.
- Feedback from the NICE clinical adviser.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research.
- Consulting with stakeholders.

- Assessing new information, topic expert feedback, stakeholder feedback and NICE clinical adviser feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered when developing the guideline

The NICE guideline on dementia (NG97) currently excludes MCI in the scope. However, the scope does include people with MCI if they are suspected of or have a confirmed diagnosis of dementia. The guideline itself did not have any specific review questions around MCI.

Information considered in previous surveillance of this guideline

There has not been previous surveillance for this guideline.

Topic expert feedback

Five topic experts were contacted by NICE and asked if there is a need for NICE guideline recommendations on MCI related to early prodromal dementia. All 5 topic experts considered that there was a need for NICE guideline recommendations on MCI. However, the experts also highlighted that MCI is a complex and heterogeneous syndrome and that not all MCI is related to dementia. The topic experts were asked to submit evidence in relation to MCI, which is discussed below in the section on submitted evidence.

Stakeholder consultation

Stakeholders were consulted and asked if they agreed with our proposal not to update the guideline. We received responses from 16 stakeholders, including NHS England, pharmaceutical companies, patient organisations and research groups. In total, 9 stakeholders disagreed with the proposal not to update the guideline at this time, 3 agreed

and 4 did not provide an answer. See appendix B for details of stakeholder comments and responses.

Of the 3 stakeholders that agreed with our proposal not to update the guideline at this time, comments generally agreed that the evidence base is still developing in MCI and updating the guidance to create consensus-based recommendations would not be a good use of NICE's resources at this time.

Of those stakeholders that did not agree with the proposal not to update, the comments largely highlighted the need for a patient pathway in MCI, biomarkers for diagnosing prodromal dementia or MCI, and new drugs for treating early dementia (NICE already has 2 technology appraisal guidance in this area as noted below). Many stakeholders also highlighted that MCI is a heterogenous and important condition and not a simple bolt on to the dementia guideline. The stakeholders also highlighted a number of published and ongoing studies, which we assessed for impact on the guideline. Relevant published studies are discussed below in the section on submitted evidence, and relevant ongoing studies are highlighted in the section on ongoing studies.

Submitted evidence

Topic experts

The topic experts were asked to submit evidence in relation to MCI. A total of 13 studies were highlighted for consideration by NICE in relation to MCI. The studies are discussed below attempting to order by overviews and reviews, then diagnosis, biomarkers, progression to dementia, interventions and finally a review of clinical guidelines.

One study presented a clinical review of MCI and reminded that this is an important area as the number of older adults increases and suggests that aerobic exercise, mental activity and cardiovascular risk factors are important interventions (Langa and Levine 2014). These interventions are currently covered by recommendations in the NICE guideline on dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset.

Another study provided an overview of MCI and stated that most MCI does not convert to Alzheimer's but provided some suggestions on neural mechanisms that may help distinguish MCI that will not progress, from MCI that will progress onto Alzheimer's (Gainotti et al. 2014).

Bassetti et al. (2022) described the European academy of neurology brain health strategy: one brain, one life, one approach. Another study described the Scottish Brain Health Service Model (Ritchie et al. 2021). Both studies cover a broad range of neurological conditions and are not specific to MCI.

One study looked at diagnosing MCI and suggested that MCI diagnoses need to incorporate more comprehensive neuropsychological methods to help identify specific cognitive phenotypes, biomarker associations, and prediction of progression (Bondi et al. 2014).

Another study aimed to investigate neuropsychological and brain metabolism features of patients with MCI and rapid eye movement (REM) sleep behaviour disorder compared with matched MCI Alzheimer's disease patients (Mattioli et al. 2022). The study found differences in neuropsychological and brain metabolism profiles, which they thought may be helpful for both diagnosis and prognosis purposes in the future.

Breton et al. (2018) undertook a meta-analysis of cognitive tests for the detection of MCI in the prodromal stage of dementia. The study found that multiple cognitive tests have comparable diagnostic accuracy but that the Memory Alteration Test is short and has the highest sensitivity. The Mini Mental State Examination (MMSE) tool had lowest sensitivity and authors suggested this should not be used as a comparison in studies of new cognitive tests.

One study was a survey in France looking at clinicians who prescribed lumber puncture to measure Alzheimer's disease cerebrospinal fluid (CSF) biomarkers which showed clinical practice in French memory clinics between 2012 to 2014 (Cognat et al. 2019).

Another longitudinal study looked at elevated plasma microRNA-206 levels to predict cognitive decline and progression to dementia from MCI and found promising results (Kenny et al. 2019).

Belleville et al. (2017) aimed to determine the extent to which cognitive measures can predict progression from MCI to Alzheimer's type dementia. The study found that predictive accuracy was highest when combining memory measures with a small set of other domains, or when relying on broad cognitive batteries.

One study undertook a review of machine learning methods for predicting progression from MCI to Alzheimer's disease (Grueso and Viejo-Sobera 2021). The authors concluded

this has potential for the future.

One study looked at multidomain interventions to improve cognition in people with MCI (Salzman et al. 2022). The study found improvements in global cognition, executive function, memory, and verbal fluency with short-term multidomain interventions (less than 1 year) compared with single interventions in older adults with MCI. However, the types of intervention and exposure varied making results difficult to interpret.

Chen et al. (2021) was a review of clinical guidelines and consensus statements around MCI, which concluded that an updated search for evidence on diagnosis and treatment of MCI is needed.

Overall, although some of the studies show some promising results, particularly around biomarkers, cognitive tests, and machine learning, unfortunately the studies do not appear to be sufficient to develop robust evidence-based NICE guideline recommendations on MCI at this time. Some of the evidence around brain health and prevention are currently covered by recommendations in the NICE guideline on dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset. One expert also noted the lack of 'quality papers' on MCI.

Stakeholders

Stakeholders were asked to submit evidence in relation to MCI. See appendix B for details of stakeholder comments and responses.

Most of the studies were not specific to MCI or simply provided more background or summary information of MCI, rather than primary research evidence that could inform the differential diagnosis or management of MCI. However, studies that are relevant to this exceptional review of MCI are briefly summarised below.

The TOMORROW RCT (Burns at al. 2021) aimed to test and qualify a biomarker risk assignment algorithm (BRAA) to identify participants at risk of developing MCI due to Alzheimer's disease within 5 years, and to evaluate the safety and efficacy of low-dose pioglitazone to delay onset of MCI (n=3,494). The study was terminated early as pioglitazone did not delay the onset of MCI. The biomarker algorithm also did not reach the pre-specified significance threshold but did demonstrate a 3 times enrichment of events in the high-risk placebo group compared with the low-risk placebo group.

One study (Blennow at al. 2019) evaluated the performance of CSF biomarkers for predicting risk of clinical decline and conversion to dementia in patients with cognitive symptoms but not diagnosed with dementia using 2 longitudinal studies (n=1,050). Aβ(1-42), tTau and pTau CSF concentrations were measured and patients were classified as biomarker-positive or biomarker-negative at baseline. The study found that risk of conversion to dementia was higher in biomarker-positive patients (hazard ratio [HR] 1.67 to 11.48). The pTau/Aβ(1–42) demonstrated the best performance for prediction of clinical decline in MCI patients over 24 months.

The ABIDE modelling study of biomarkers (Maurik et al. 2019) aimed to establish robust prediction models of disease progression in people at risk of dementia. The study included data from 4 cohort studies (n=2,611 people with MCI). The study found that the validated demographics model (Harrell's C 0.62, 95% confidence interval [CI] 0.59 to 0.65), validated hippocampal volume model (0.67; 95% CI 0.62 to 0.72), and updated CSF biomarkers model (0.72; 95% CI 0.68 to 0.74) had adequate prognostic performance across cohorts and were well calibrated. The newly constructed ATN model had the highest performance (0.74; 95% CI 0.71 to 0.76). The authors concluded that future research should focus on the clinical utility of the models, particularly if their use affects a person's understanding, emotional wellbeing, and behaviour.

Another study (McKeith et al. 2020) looked at whether there is sufficient information to justify a diagnostic criteria for the prodromal phase of dementia with Lewy bodies, looking at MCI, delirium-onset, and psychiatric-onset presentations. The review found insufficient evidence to propose formal criteria for delirium-onset and psychiatric-onset presentations but propose diagnostic criteria for probable MCI with Lewy bodies, which are intended for use in research settings.

The LipiDiDiet trial (Soininen et al. 2021) looked at the effects of a specific multi-nutrient combination Fortasyn Connect (125 mL once-a-day Souvenaid drink) versus placebo drink on cognition and related measures in prodromal Alzheimer's disease. Over 36 months, the trial found significant reductions in decline were observed for the Neuropsychological Test Battery 5-item composite (-60%; p=0.014), Clinical Dementia Rating-Sum of Boxes (-45%; p=0.014), and memory (-76%; p=0.008). The authors concluded that the multi-nutrient intervention slowed decline in cognition and disease progression. However, a Cochrane review (Burckhardt et al. 2020) of Souvenaid for Alzheimer's disease found that 2 years of treatment with Souvenaid probably does not reduce the risk of progression to dementia in people with prodromal Alzheimer's disease. However, conflicting evidence on combined cognitive-functional outcomes in prodromal Alzheimer's disease and mild Alzheimer's

disease dementia were deemed to warrant further investigation.

The FINGER trial (Ngandu et al. 2015, Rosenberg et al. 2018) was a proof of concept RCT (n=2,654 people aged 60 to 77 years) of a multimodal intervention (diet, exercise, cognitive training, vascular risk monitoring), compared with a control group (general health advice). The trial found that between-group differences in comprehensive neuropsychological test battery Z score significantly favoured the comprehensive intervention (per year change in score was 0.022, p=0.030). The World-Wide FINGERS (WW-FINGERS) network programme of research was then developed to investigate the multimodal intervention in other populations and diverse cultural and geographical settings (Rosenberg et al. 2020). This research programme will be tracked (see ongoing studies).

One study (Jiang at al. 2023) examined the association between hearing aid use and risk of dementia in middle-aged and older adults using the UK biobank. The analysis found a 42% increased risk of dementia in people with self-reported hearing loss compared with those without (HR 1.42; 95% CI 1.28 to 1.57), but no increased risk in those who used hearing aids. However, confounding could not be ruled out as participants who used hearing aids may be different than those who do not, such as more health aware, or more affluent, which could have influenced results.

Overall, the evidence submitted by stakeholders was not deemed sufficient to develop robust evidence-based NICE guideline recommendations at this time. However, because this topic is important to our stakeholders, we will refer it to our new topic prioritisation board for consideration.

Ongoing research

A search for ongoing research and stakeholder consultation identified the following:

- Interceptor project: From MCI to dementia: NCT03834402 (study completion estimated Dec 2023)
- TRC-PAD Program In-Clinic Trial-Ready Cohort: NCT04004767 (study completion estimated April 2024)
- MRI and PET Biomarkers for Cognitive Decline in Older Adults NCT03860857 (study completion estimated Dec 2024)

- Clinical validation and commercialisation of the ReaCTIVE app: A proactive, interactive cognitive monitoring and intervention solution for people with early cognitive impairment (study completion unclear)
- PrAISED2 study: promoting activity, independence and stability in early dementia (study completion estimated January 2023)
- Mysmile study: oral health for brain health (study completion unclear)
- World Wide FINGERS Network has a programme of research, including the US POINTER study and the AU-Arrow study and the 10-year follow-up of FINGERS (study completion unclear).

These studies will be added to the NICE event tracker and assessed once results become available.

Internal NICE clinical adviser assessment

NICE has a clinical directorate that provides clinical advice and expertise across NICE and considers which topics add most value to the health and care system. Clinical advice was sought on this topic that noted the lack of robust evidence in the area to make evidence-based recommendations. As such, it was considered too early to support a scope expansion of the NICE dementia guideline to cover MCI.

Other relevant NICE guidance

NICE has a quality standard on dementia, which covers preventing dementia, and assessment, management and health and social care support for people with dementia. NICE also has a guideline on dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset, which covers mid-life approaches to delay or prevent the onset of dementia, disability and frailty in later life.

There are 2 NICE technology appraisals in development (publication dates to be confirmed):

- Donanemab for treating MCI or mild dementia caused by Alzheimer's disease [ID6222]
- Lecanemab for treating MCI or mild dementia caused by Alzheimer's disease [ID4043]

Equalities

An equalities and health inequalities assessment was completed during this surveillance review. See appendix A for details.

Overall decision

We will not update the guideline on dementia. However, because this topic is important to our stakeholders, we will refer it to our new topic prioritisation board for consideration.

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