

# HEIGHTS

## The role of the Gut Microbiome in Healthy Cognitive Ageing



Biotechnology and  
Biological Sciences  
Research Council



INFORM Hub



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# Terminology

**Dementia:** A group of progressive brain conditions that affect memory, thinking and daily functioning. Alzheimer's disease is the most common type.

**Cognitive Function:** Mental abilities such as memory, attention, learning, reasoning and decision-making.

**Mental Cognitive Impairment (MCI):** Early problems with memory or thinking that are noticeable but do not yet severely disrupt daily life. MCI increases the risk of developing dementia.

**Gut Microbiome:** The community of trillions of microorganisms living in the digestive system that support digestion, immunity and overall health.

**Gut-Brain Axis:** The two-way communication system between the gut and the brain, through which gut bacteria may influence brain health and behaviour.

**Probiotics:** Live beneficial bacteria intended to support gut health.

**Prebiotics:** Dietary fibres that feed beneficial gut bacteria and help them grow.

**Synbiotics:** Products that combine probiotics (live bacteria) and prebiotics (their food) in one intervention.

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## Terminology Continued

**Randomised Controlled Trial (RCT):** A high-quality study design where participants are randomly assigned to receive either an intervention (e.g. a probiotic) or a placebo.

**Systematic Review:** A structured summary of all relevant research studies on a topic, using predefined methods to reduce bias.

**Meta-analysis:** A statistical method that combines results from multiple studies to estimate an overall effect.

**Effect Size:** A measure of how large an intervention's impact is. In this report, it reflects the average improvement in cognitive outcomes.

**MMSE (Mini-Mental State Examination):** A widely used clinical test that assesses cognitive function and helps classify the severity of cognitive impairment.

**Quality-Adjusted Life Year (QALY):** A measure combining quality and length of life:

- 1 QALY = 1 year in full health
- 0.5 QALY = 1 year in half-good health (or 6 months in full health)

**Incremental Cost-Effectiveness Ratio (ICER):** The additional cost required to gain one extra QALY compared with current care.

**Willingness-to-Pay Threshold:** The amount the NHS typically considers acceptable to pay for one QALY (£20,000–£30,000).

# Executive Summary

Dementia represents a major and growing public health challenge in the United Kingdom, with profound impacts on quality of life for individuals, families and carers, and substantial costs to health and social care systems. In the absence of disease-modifying treatments, there is an urgent need to identify accessible, low-risk interventions that can support cognitive function and wellbeing and contribute to dementia prevention and care strategies.

Emerging evidence suggests that the gut microbiome plays a crucial role in cognitive health through the gut-brain axis, sparking interest in microbiome-modulating interventions, such as probiotics. This report synthesises current scientific evidence linking gut microbiome modulation to cognitive outcomes and evaluates the potential value for money of probiotic supplementation when delivered at scale.

A systematic review and meta-analysis of published randomised controlled trials demonstrates small but statistically significant improvements in cognitive outcomes associated with microbiome-modulating interventions, particularly probiotics. Subgroup analyses suggest that effects may vary by intervention duration, population characteristics and intervention type. Conservative economic modelling indicates that probiotic supplementation can deliver measurable gains in quality-adjusted life years at a cost well within commonly applied value-for-money thresholds, even under cautious assumptions in those with pre-existing cognitive deficits.

Taken together, the findings suggest that microbiome-modulating interventions may represent a feasible, scalable and cost-effective approach to supporting cognitive wellbeing, with potential relevance for future dementia prevention and care policy.

# Key Findings

The gut microbiome is increasingly recognised as a modifiable factor linked to cognitive function through the gut-brain axis

Subgroup analyses indicate that longer intervention durations and specific population groups may experience greater benefits.

A systematic review and meta-analysis of randomised controlled trials identified small but statistically significant improvements in cognitive outcomes associated with microbiome-modulating interventions.

Economic modelling suggests that probiotic supplementation can deliver quality-of-life gains at a cost per QALY well below commonly used willingness-to-pay thresholds.

Probiotic supplementation showed consistent positive effects on cognition, while evidence for prebiotics and synbiotics remains more limited.

At a population level, modest individual effects could translate into meaningful cumulative improvements in wellbeing if implemented at scale.

# Background

## Burden of Dementia

Dementia is an umbrella term for a number of brain diseases that are characterised by a progressive decline across multiple cognitive domains, with profound effects on independence, wellbeing and quality of life. With Alzheimer's Disease being the most common cause of Dementia, account for 70% of Dementia cases. In the United Kingdom, approximately 982,000 people are currently living with dementia, and whilst not an evitable part of ageing lifetime incidence estimates suggest that around one in three individuals will develop dementia. Intervention options remain limited. At present, there are very few disease-modifying treatments available, and commonly used medications offer only temporary symptomatic relief without addressing the underlying pathophysiology. This gap highlights the importance of identifying preventative approaches that can reduce the incidence of dementia or delay its onset.



Unless effective action is taken to prevent dementia, the number of people living with dementia is projected to increase to 1.4 million by 2040. A growing body of research highlights the role of modifiable risk factors, including diet, physical activity and metabolic health, in shaping cognitive ageing trajectories. These factors are increasingly recognised as central targets within public health policy. The most recent Lancet report on prevention and care estimates that up to 45 per cent of dementia cases could be prevented or delayed through effective modification of known risk factors. Taken together, these insights reinforce the need to advance accessible and scalable interventions that can promote cognitive health throughout adulthood older age.

## Evidence suggesting a link between the gut microbiome, cognitive function and dementia

The idea that digestive health influences wider aspects of human physiology has ancient origins, with Hippocrates noting more than 2,000 years ago that “all disease begins in the gut”. Only recent advances in sequencing technologies, microbial ecology and immunometabolic science have enabled detailed investigation of the gut microbiome and its relationship with brain function. This bidirectional communication network, often referred to as the gut–brain axis, has become an active area of research due to emerging associations between microbiome composition and neurological outcomes.

**Observational studies** have reported that reduced microbial diversity and specific compositional profiles are associated with poorer cognitive performance and increased dementia risk, independent of conventional risk factors. These findings have stimulated interest in microbiome-modulating interventions, including prebiotics, probiotics and synbiotics, as potential tools for supporting cognitive function.

Randomised controlled trials provide early evidence to support this hypothesis. In healthy older adults, ten weeks of multi-strain probiotic supplementation produced measurable improvements in cognitive performance compared with placebo.



In individuals with suspected mild cognitive impairment, sixteen weeks of single-strain probiotic supplementation has been associated with improved memory. Although further work is required to understand long-term effects, the durability of benefits and strain-specific responses, these results suggest that the gut microbiome may represent a modifiable factor capable of influencing day-to-day cognitive function. Importantly, such interventions can be delivered at low cost, require minimal clinical infrastructure and may be suitable for population-level implementation.

## Why this topic matters for policy, the NHS and wider society

The societal and economic burden of dementia is substantial. Current estimates place the annual cost to the UK economy at approximately £42.5 billion. This includes direct NHS costs of around £7.1 billion, social care expenditure of £17.2 billion and the significant economic value of unpaid informal care, estimated at £21.1 billion. As life expectancy rises, the number of people living with dementia is projected to increase markedly, with total economic costs expected to exceed £90 billion by 2040.

Even modest reductions in dementia risk or small improvements in day-to-day wellbeing in those living with the condition could therefore generate meaningful individual, societal and economic benefits. This challenge has been recognised in several government initiatives, including the Prime Minister's Challenge on Dementia 2020 and the subsequent Dementia Goals programme, which emphasise risk reduction, earlier intervention and the translation of research into practice. Consequently, there is a strong policy imperative to identify preventative measures and interventions that are evidence-based, cost-effective and feasible to implement at scale in order to support those living with or at risk of developing dementia.

Growing evidence suggests that the gut microbiome may play a causal role in pathways relevant to cognitive decline and

dementia. Given the positive findings from randomised trials of probiotic supplementation, and their potential integration into existing primary and community care pathways, microbiome modulation may represent a low-cost and accessible component of broader dementia prevention and care strategies.

## Positioning the economic modelling within this report

The economic modelling protocol was informed by a critical appraisal of the findings from the systematic review and meta-analysis conducted as part of this report (discussed below). To ensure the development of a scientifically robust and accurate economic model, a conservative approach was adopted, with the model focusing on gains in quality-adjusted life rather than direct NHS cost savings. This decision reflects the current limitations of the available evidence and the modelling team's cautious approach in avoiding assumptions about long-term disease progression, healthcare utilisation, or dementia risk reduction that cannot yet be substantiated empirically. The model, therefore, examines whether improving day-to-day quality of life for people living with dementia, through symptomatic benefits observed in clinical trials, would represent good value for money if delivered at a national scale. This framing provides an appropriate and robust foundation for interpreting the results presented later in the report.

# Objectives of the report

**This report brings together scientific and economic evidence to provide a comprehensive and accessible assessment for policy makers, healthcare professionals and industry partners. Specifically, the objectives are to:**

- Consolidate current evidence on the relationship between the gut microbiome, cognitive function and dementia risk
- Synthesise results from randomised controlled trials of microbiome-modulating interventions
- Present economic modelling that evaluates the potential value for money of implementing such interventions at scale, based on quality-of-life gains
- Support informed decisions about whether gut microbiome modulation could contribute to future public-health approaches to dementia prevention
- Stimulate discussion about next steps for research, evaluation and policy development.



By integrating these strands of evidence, the report aims to provide a clear foundation for considering how gut-modulating interventions could contribute to dementia prevention and the improvement of day-to-day wellbeing for people living with the condition in the United Kingdom.

# Methodology

## Systematic review and meta-analysis

A systematic review and meta-analysis was conducted to synthesise evidence from randomised controlled trials examining the effects of gut microbiome-modulating interventions on cognitive outcomes. Searches were undertaken across three electronic databases using predefined search terms relating to cognition, dementia and microbiome-modulating interventions, including probiotics, prebiotics and synbiotics (detailed in Appendix 1).

Studies were eligible for inclusion if they involved adult participants, employed a randomised controlled trial design, and reported validated cognitive outcomes (Appendix 2). Data were extracted on participant characteristics, intervention type and duration, and cognitive outcome measures. Where appropriate, results were pooled using meta-analytic techniques to estimate overall effects on cognitive performance.

Pre-specified subgroup analyses were conducted to explore potential sources of heterogeneity, including age group, disease severity, intervention duration and type of microbiome-modulating intervention.

## Economic modelling methods

An economic evaluation was undertaken to assess the potential value for money of introducing probiotic supplementation as an adjunct to current care for people living with dementia in the United Kingdom. In light of the current evidence base, the modelling adopted a deliberately conservative approach and focused on estimating gains in quality-adjusted life years (QALYs), rather than attempting to quantify direct cost savings to the NHS.

A cohort-based model was used to compare current care alone with current care plus daily probiotic supplementation over a five-year programme horizon, reflecting a realistic timeframe for a national pilot or early implementation phase. The eligible population comprised all people diagnosed with dementia in the UK. Programme uptake was assumed to increase from approximately 50 per cent to 65 per cent over the first two years before plateauing, with an annual dropout rate of 12 per cent applied to reflect declining engagement over time.

Health outcomes were expressed in QALYs, with observed changes in cognitive function from randomised controlled trials conservatively mapped to quality-of-life gains.

Costs included probiotic procurement and delivery alongside existing dementia-related care costs. However, programme start-up and implementation overheads were not explicitly modelled given the NHS infrastructure to deliver public health interventions at low cost and at scale already exists and can be leveraged for the purposes of this programme. Additional infrastructure investments were considered negligible and well within the budgetary headroom of a cost-effective intervention. All costs and outcomes were discounted in line with standard UK health economic practice.

The primary outcome was the incremental cost-effectiveness ratio (ICER), expressed as the additional cost per QALY gained compared with current care alone. Sensitivity analyses explored uncertainty around key parameters, including probiotic price, uptake and adherence. Modelling outputs are presented in Figures 2 to 6 and interpreted in the results and discussion sections.

An in-depth protocol for the economic analysis, including the specific model used, assumptions, limitations of the modeling and key uncertainties can be found in Appendix 3.

## What is a QALY?

A “**QALY**” (quality-adjusted life year) is a standard way of combining the **Length** and **Quality** of life into a single measure.

**1 QALY** = 1 year of life in full health.

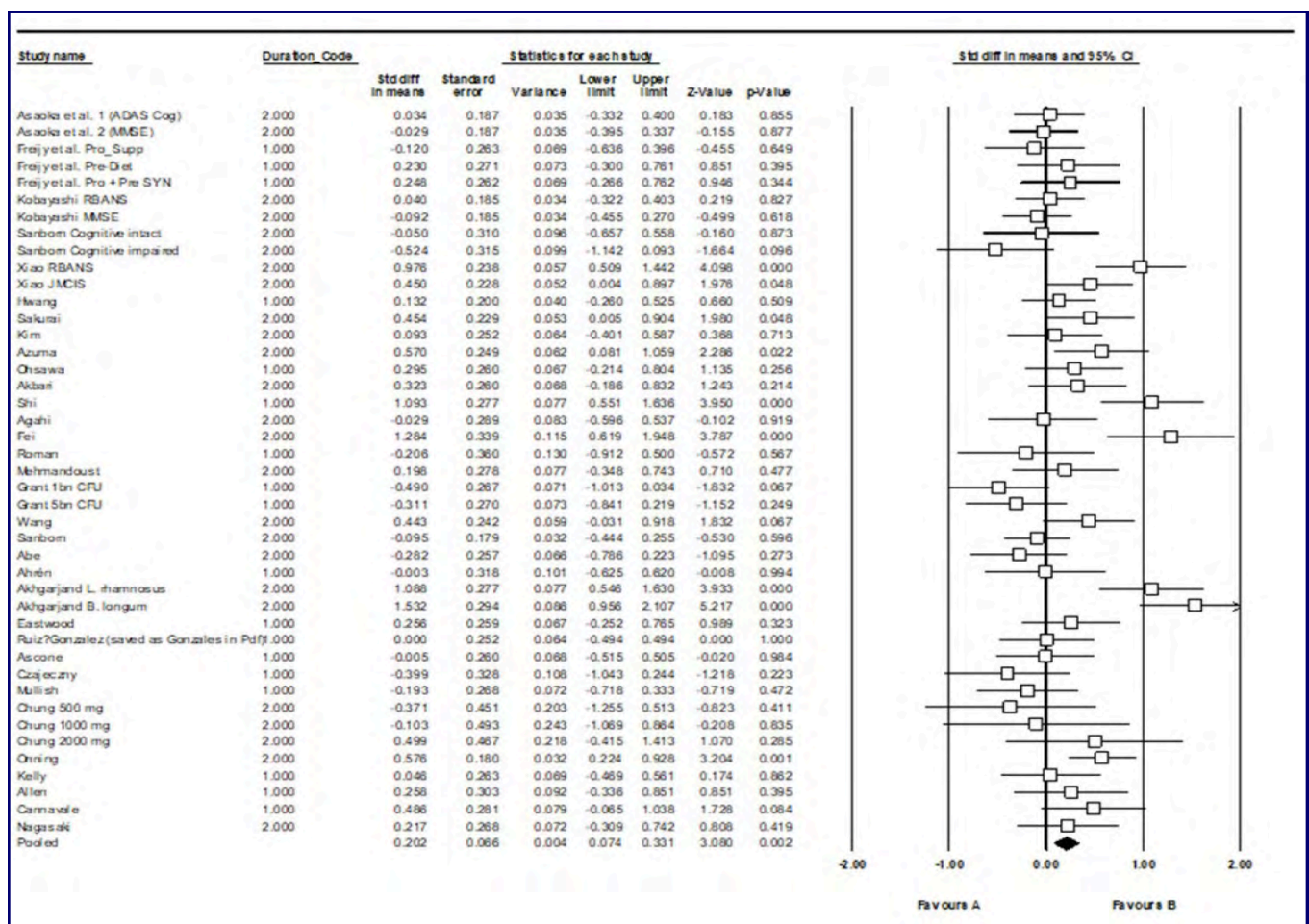
**0.5 QALYs** = could be 1 year in half-good health OR 6 months in full health



# Results

## Evidence synthesis - Meta-analysis Outcome

The systematic review and meta-analysis included 33 randomised controlled trials examining the effects of microbiome-modulating interventions on cognitive outcomes across a range of populations and settings. Appendix 4 provides a detailed table of the trials included within the meta-analysis. When results were pooled, microbiome-modulating interventions were associated with a small but statistically significant improvement in cognitive performance (Figure 1).



**Figure 1.** Forest plot of the overall effect of probiotics on cognition in a random-effects model. The random-effects meta-analysis reported a small but statistically significant overall effect of the intervention on cognitive outcomes (Hedges'  $g = 0.20$ , 95% CI 0.07 to 0.33,  $p = 0.003$ ).

# Results

Considerable heterogeneity was observed between studies, reflecting differences in participant characteristics, intervention duration and cognitive outcome measures. Subgroup analyses suggested that intervention duration may be an important determinant of effectiveness, with longer interventions generally associated with greater cognitive benefits. Effects also varied by population group, with stronger improvements observed in older adults.

When examined by intervention type, probiotic supplementation demonstrated a consistent positive association with cognitive outcomes. Evidence for prebiotics and synbiotics was more limited, largely due to the smaller number of available studies. While individual effect sizes were modest, the consistency of findings across diverse studies supports the biological plausibility of a link between gut microbiome modulation and cognitive function.

The subgroup analysis based on health status indicated a trend towards a positive benefit of gut microbiome modulating interventions in healthy adults. Whereas, stronger evidence of an effect was found in those individuals with compromised cognition at baseline (Figure 2)

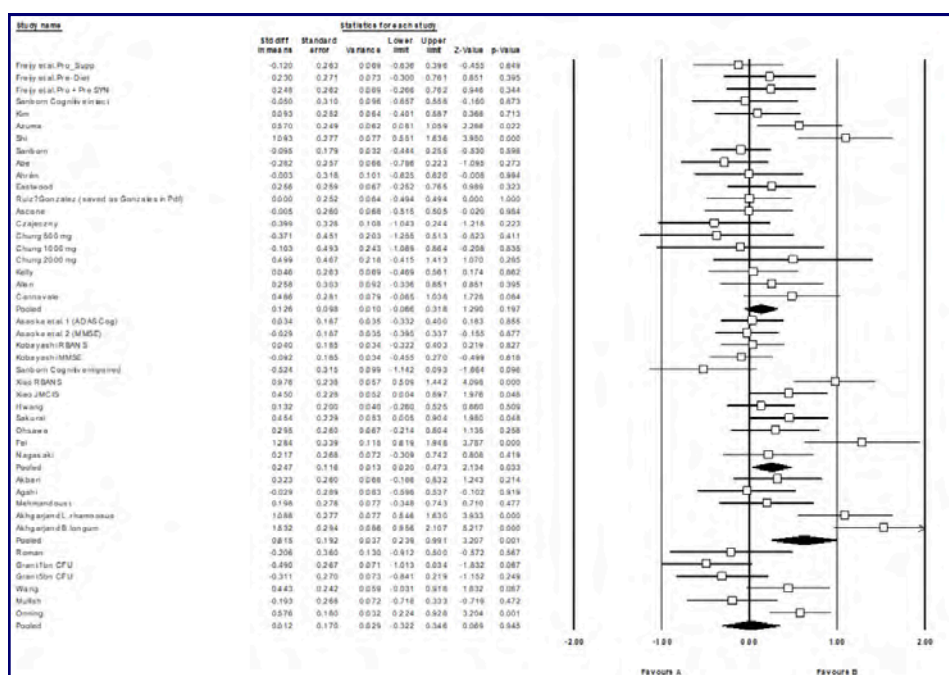


Figure 2. Forest plot of the effect of probiotics on cognition in a random-effects model based on cognitive state at baseline. Where A = Placebo, B = Active.

## 14.

The subgroup analysis reported a trend towards a significant beneficial effect of the intervention on cognition in healthy participants. A statistically significant beneficial effect of the intervention on cognitive outcomes was reported for individuals diagnosed with Mild Cognitive Impairment or Alzheimer's Disease at baseline. Where 1 = Cognitively healthy, 2 = MCI, 3 = Alzheimer's Disease and 4 = Other diagnosed medical conditions (e.g. irritable bowel syndrome).

A critical appraisal of the meta-analysis evidence, alongside the practical relevance of the economic modelling, indicated that restricting analyses to individuals with baseline cognitive impairment offers the most robust and policy-relevant assessment of the population-level utility of gut microbiome modulation for supporting cognitive health. Below, we outline how the meta-analysis results were incorporated into the economic modelling assessment.

### **Evidence synthesis - Combining Meta-analysis results into the Economic Model**

To inform the economic modelling, subgroup analyses were conducted, specifically on trials that reported the MMSE as an outcome in response to gut microbiome modulating interventions, split by cognitive status at baseline. This approach was chosen since the MMSE is the most widely

reported cognitive assessment tool and has the strongest mapping to cognitive utilities at the population level.

This cognitive assessment tool is also widely used in clinical practice and incorporates defined thresholds indicating mild, moderate and severe cognitive deficits.

The following MMSE thresholds were used to define cognitive impairment severity status:

**Mild dementia: MMSE = 26 – 21**

**Moderate dementia: MMSE = 20 – 10**

**Severe dementia: MMSE = <10**

The results from the meta-analysis indicated a pooled mean difference of 2.90 points for mild cognitive impairment, 4.03 for moderate cognitive impairment and 2.37 for severe cognitive impairment (Figure 3). The severe-stage estimate was not statistically significant thus a zero effect was assumed for severe dementia in the base case, with the full uncertainty interval explored in sensitivity analyses. These MMSE gains were mapped to EQ-5D-compatible utility changes using conservative slopes derived from published datasets linking cognition and utilities in dementia (Keetharuth 2022, Hussain 2022, Rombach 2021, Martin 2019, Wolfs 2007).

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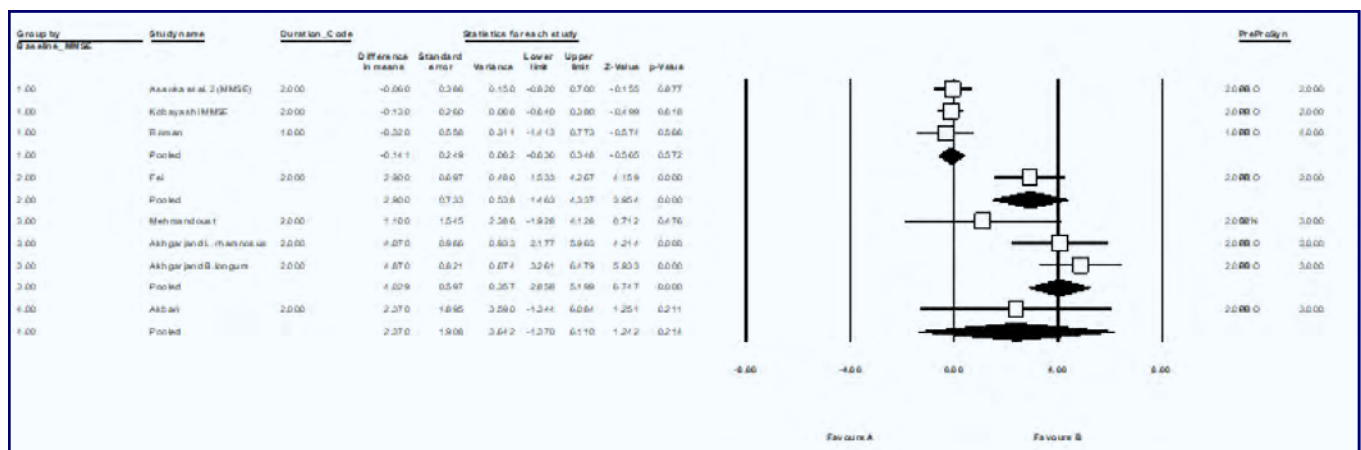
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**Figure 3.** Forest plot of the effect of probiotics on MMSE score in a random-effects model based on cognitive state at baseline. Where A = Placebo, B = Active.

### Evidence synthesis - Combining Meta-analysis results into the Economic Model

To inform the economic modelling, subgroup analyses were conducted, specifically on trials that reported the MMSE as an outcome in response to gut microbiome modulating interventions, split by cognitive status at baseline. This approach was chosen since the MMSE is the most widely. The results of the economic modeling indicated that a probiotic programme rolled out across the UK population could:

- Deliver more years of good-quality life for people with dementia, because their quality of life is assumed to be improved while they are on the supplement.
- Costs the system more overall than current care alone, because the NHS has to purchase and distribute the probiotic and no cost savings are assumed.



## 16.

In summary, the probiotic programme increases total discounted costs by approximately £159m. This additional cost represents <1% of the total societal cost of dementia over this period (approximated at £229.9bn). At the same time, the programme is assumed to yield an additional **34,000 QALYs**. This corresponds to an incremental cost-effectiveness ratio (ICER) of **£4,702 per QALY gained**, well below the commonly used willingness-to-pay range (£20,000–£30,000/QALY) that the NHS applies when assessing drugs and public health programmes for reimbursement.

The programme itself is estimated to cost approximately £1.10 per week per person on the programme (£57–58 per year). At the level of the individual, the model suggests that this small weekly investment in the probiotic buys a modest but real improvement in quality of life each year - about 4 extra days of good-quality life per year. For every 1,000 people on the programme, this equates to over 4,000 additional “good-health” days annually.

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Total nominal programme spend over five years is projected at approximately £170m, with annual costs rising from £27m in year 1 to approximately £38m in year 5 as uptake increases and the dementia population grows. Taken together, this represents <1% of the annual Public Health Grant allocated to local authorities in England, implying a modest budget impact at system level.

Appendix 5 provides further information in relation to the inputted economic modeling variables. A detailed description of the economic modelling findings is provided in Appendix 6.

# Discussion

## Interpretation of findings from the systematic review and meta-analysis

The findings of the systematic review and meta-analysis provide important context for interpreting the potential role of microbiome-modulating interventions in dementia prevention and care, with evidence of a small but statistically significant improvement in cognitive outcomes, particularly for probiotics. Although the observed improvements in cognitive outcomes were modest at the individual level, they were consistent across a diverse evidence base and statistically robust. Importantly, the magnitude of these effects is comparable to those observed for other non-pharmacological interventions currently recommended within dementia care pathways, such as physical activity and exercise programmes.

Subgroup analyses suggest that intervention characteristics and population factors may influence effectiveness. In particular, longer intervention durations appeared to be associated with greater cognitive benefits, highlighting the importance of sustained engagement. Differences observed between intervention types further suggest that probiotics may represent the most microbiome-modulating approach at



at present, although further research is needed to clarify optimal formulations and dosing strategies.

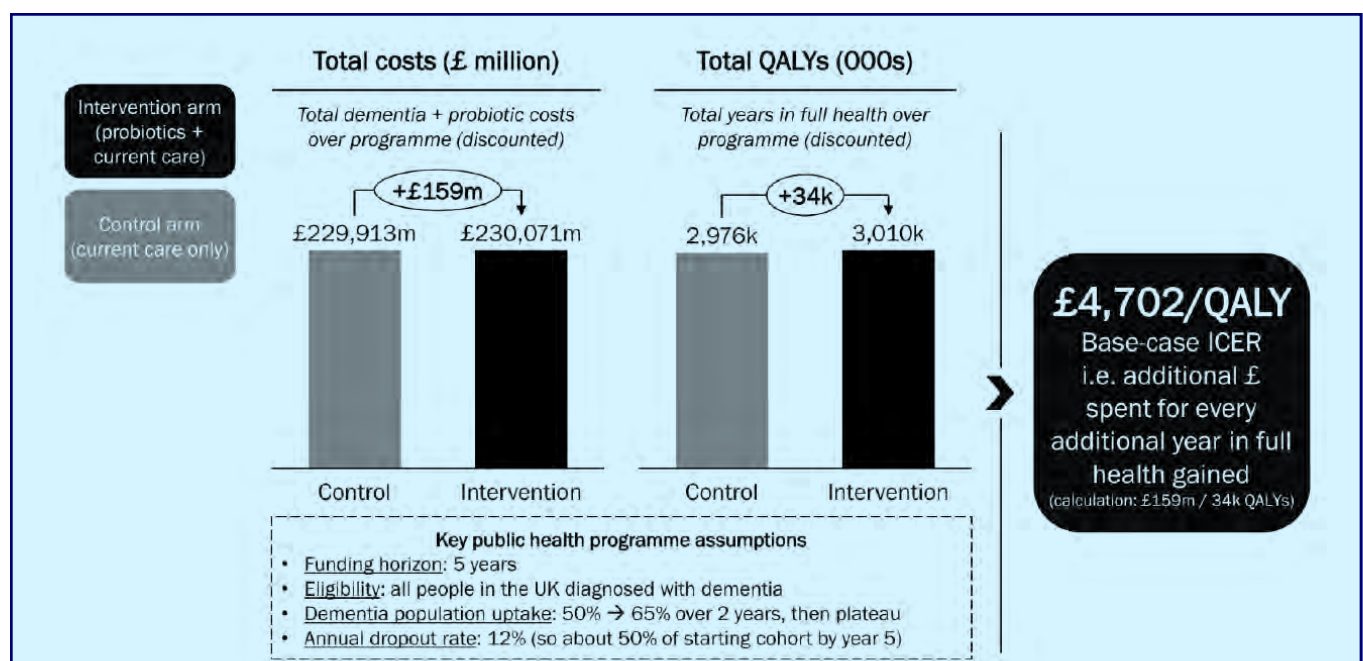
From a public health perspective, modest improvements in cognitive function can be meaningful when applied at scale. These findings provide a strong scientific rationale for exploring the feasibility and value of microbiome-modulating interventions through pilot programmes and real-world evaluations, and they underpin the assumptions used in the economic modelling presented later in this report.

# Recommendations for policy and practice

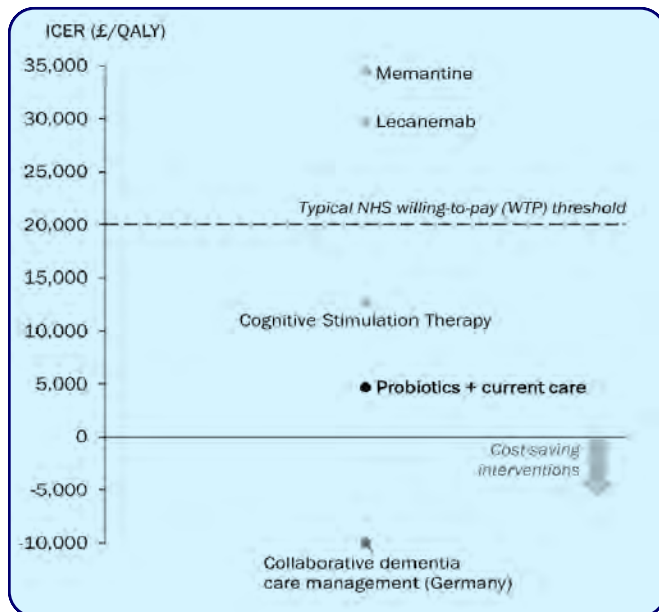
Comparison of total discounted costs and quality-adjusted life years (QALYs) between current care alone and current care plus probiotic supplementation over a five-year programme horizon. The base-case incremental cost-effectiveness ratio (ICER) indicates the additional cost per QALY gained for the intervention arm.

The evidence reviewed in this report suggests that gut-modulating interventions, particularly probiotic supplementation, may offer a low-cost and accessible means of improving day-to-day cognitive wellbeing in people living with dementia. Although the current trial literature is still developing, the consistent pattern of modest cognitive benefits and the favourable cost-effectiveness profile identified through economic modelling support the case for further evaluation within real-world health systems (see Figure 4 and 5).

Figure 4. Summary of economic model outputs



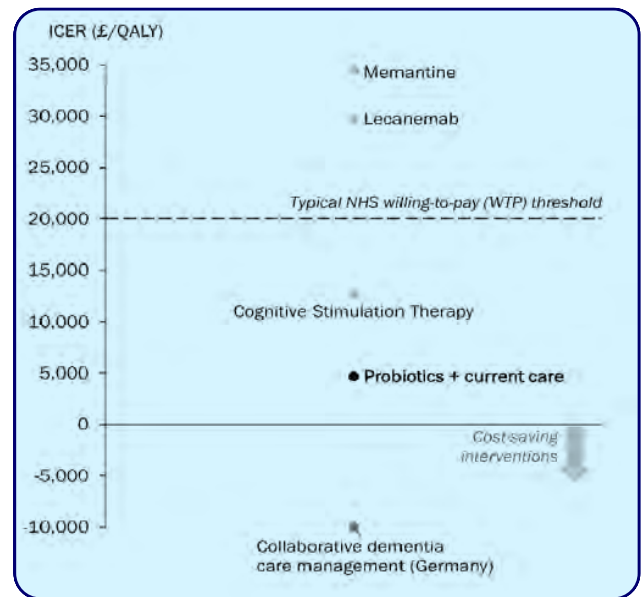
A practical first step would be the establishment of a national, time-limited pilot programme in which an evidence-based probiotic formulation is offered to people with a diagnosis of dementia. This programme should be delivered through existing pathways such as primary care dementia reviews, memory clinics, community mental health teams and community pharmacies. Clear, accessible patient and carer information would be required to communicate what probiotics can and cannot do, how they should be taken, and how to report any issues.



**Figure 5.** Comparative cost-effectiveness of dementia interventions. Incremental cost-effectiveness ratios for probiotic supplementation compared with selected dementia treatments and care models, benchmarked against the commonly applied NICE willingness-to-pay threshold.

To ensure consistency across the system, the probiotic products used should match the formulations evaluated in clinical trials in terms of strain composition and dose.

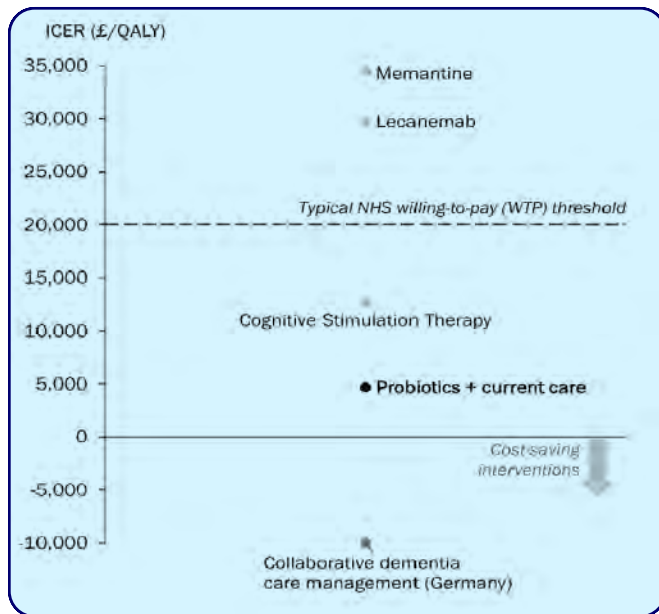
National procurement mechanisms would help secure quality assurance and favourable pricing, while preventing unnecessary variation between local areas (see Figure 6).



**Figure 6.** Probiotic price thresholds and sensitivity analysis.

Embedding adherence support into routine care would maximise the likelihood of benefit. Practical tools, such as calendar packs, reminder prompts, or synchronising supplementation with existing medications, could be co-designed with people living with dementia and their caregivers (Figure 7). Finally, the pilot should be explicitly evaluative, with clear criteria for continuation, scale-up, modification or cessation based on real-world uptake, adherence, quality of life outcomes and any emerging service-use data.

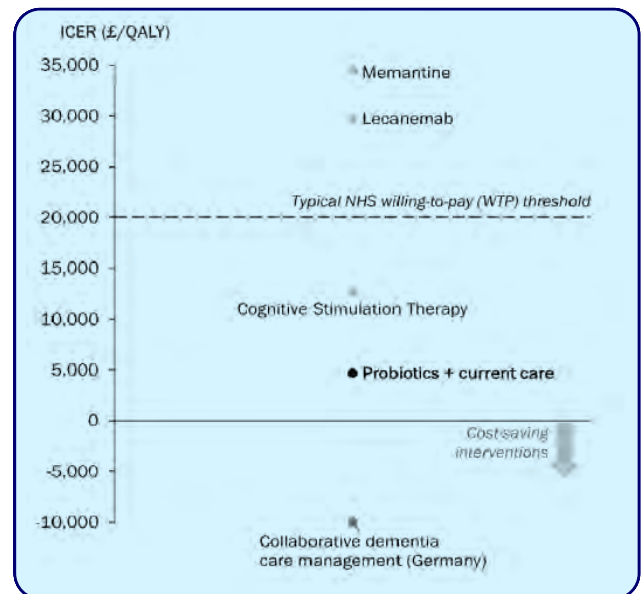
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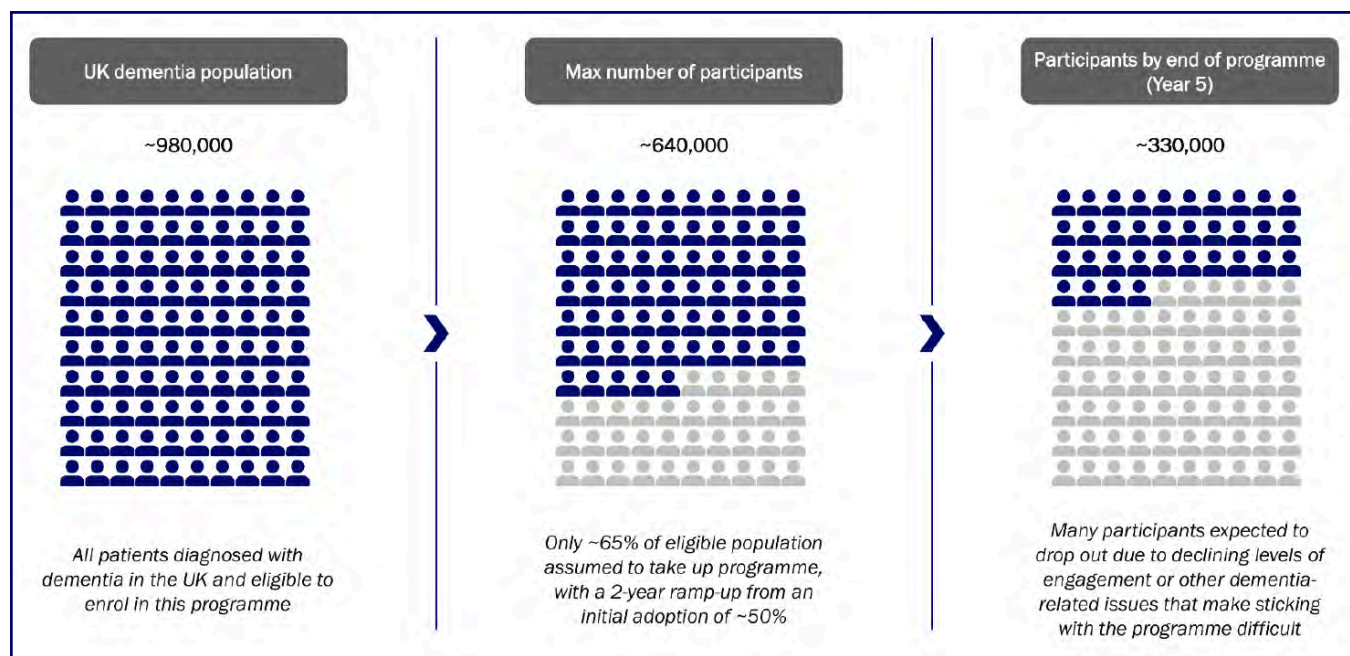
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**Figure 6.** Probiotic price thresholds and sensitivity analysis. Relationship between probiotic price and ICER under base-case, conservative and optimistic modelling scenarios, highlighting pricing ranges consistent with cost-effectiveness thresholds.

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**Figure 7.** Programme uptake and attrition assumptions. Estimated eligible population, uptake trajectory and participant retention over the five-year programme, reflecting conservative assumptions about adoption and dropout in people living with dementia.

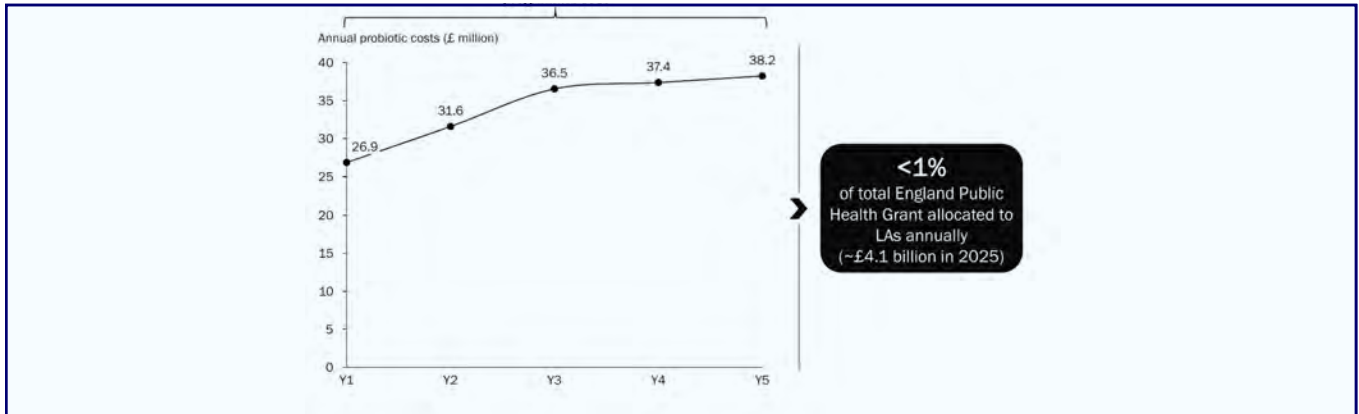
## Policy levers and intervention points

Several existing policy mechanisms could support implementation if the evidence continues to strengthen:

- **National guidance: NICE dementia guidelines** or complementary national standards could include probiotics as a supportive option, with careful wording on evidence strength and appropriate use.
- **Primary care and pharmacy contracts:** Dementia reviews, structured medication checks, or community pharmacy services could incorporate the offer, counselling, initial supply and follow-up.

- **Public health and prevention budgets:** Given the low per-person cost and potential population benefit demonstrated in the modelling (Figure 8), probiotics could be funded within prevention or long-term condition budgets managed by Integrated Care Boards or local authorities.
- **Research and innovation frameworks:** INFORM Hub partners, academic groups and industry stakeholders could use this pilot as a platform for further translational research into microbiome-based interventions.

These levers would enable a coordinated and equitable approach while giving local systems flexibility to tailor delivery to population needs.



**Figure 8.** Annual programme costs. Projected annual costs of delivering probiotic supplementation nationally over five years, demonstrating affordability relative to existing public health expenditure.

## Considerations for implementation

Successful implementation requires attention to several practical factors:

### Eligibility:

Early implementation may focus on people with mild-to-moderate dementia living in the community, where evidence is strongest and adherence is easier to support.

### Equity:

Monitoring uptake by age, ethnicity, socioeconomic status and living situation will be crucial to ensure that benefits are distributed fairly and that no groups are unintentionally excluded.

### Supply and logistics:

National contracting should ensure reliable supply chains, consistent packaging and stable product availability to avoid interruptions that could compromise adherence.

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National contracting should ensure reliable supply chains, consistent packaging and stable product availability to avoid interruptions that could compromise adherence.

### Data and evaluation:

Systems for recording uptake, adherence, adverse events and patient-reported outcomes should be incorporated into GP and pharmacy records in accordance with data protection and consent standards.

### Integration with existing care:

Supplementation should complement, not replace, current dementia support. Clinicians and care teams will require brief guidance on which products to offer and how to explain their purpose.

These considerations are vital for ensuring that any large-scale programme is feasible, safe and acceptable to patients, carers and professionals.

# Risks and mitigating factors

**While the evidence is promising, several uncertainties need to be acknowledged:**

**Uncertain long-term benefit:** Most trials are short in duration. A time-limited but well-evaluated pilot would provide real-world longitudinal data to assess the durability of effects.

**Adherence challenges:** People with dementia already manage complex routines. Simple dosing schedules, integration with existing medications, and carer-supported tools can help maintain adherence.

**Product variability:** Not all commercially available probiotics match the strains or doses used in research. National procurement and clear prescribing protocols can prevent product substitution or confusion.

**Opportunity cost:** Any investment in probiotics should be periodically reviewed against competing priorities. Explicit evaluation criteria will support proportionate decision-making (Figure 3).

**Safety considerations:** Probiotics are generally safe but may not be suitable for people with severe immunosuppression or certain gastrointestinal conditions. Simple screening and monitoring will limit this risk.

## Impacts and future directions

In the short term, this report provides a clear and policy-relevant synthesis of scientific and economic evidence that can inform national and local discussions on dementia prevention and supportive care. The economic modelling demonstrates that probiotic supplementation is likely to deliver measurable gains in quality of life at a cost well within commonly applied value-for-money thresholds, even under conservative assumptions (Figures 2 and 3). This strengthens the case for consideration within policy development, commissioning discussions and the design of pilot programmes.

A useful parallel can be drawn with the implementation of Cognitive Stimulation Therapy (CST), an intervention that demonstrated modest individual-level benefits in early trials but was subsequently adopted into routine practice due to its favourable cost-effectiveness, scalability and acceptability. As with probiotics, CST was not introduced on the basis of disease modification, but rather on its ability to deliver meaningful improvements in quality of life at the population level. This precedent illustrates how interventions with relatively small per-person effects can still justify implementation when they are low risk, affordable and deliverable

through existing care pathways. In this context, the modelling presented in this report suggests that probiotic supplementation may warrant similar consideration as a supportive intervention within dementia care, subject to further evaluation.

Over the longer term, if such interventions were implemented at scale following further evaluation, the economic modelling suggests that cumulative gains in quality-adjusted life years could be substantial, even where individual benefits remain modest. Importantly, the modelling indicates that these gains are achieved at a cost per QALY well below commonly applied willingness-to-pay thresholds, and at an overall programme cost that remains small relative to existing public health expenditure. This combination of affordability and value for money underpins the potential for population-wide delivery without placing disproportionate pressure on health system budgets. Population-wide delivery could generate substantial cumulative gains in wellbeing for people living with dementia, while remaining affordable within existing public health budgets (Figure 4). A phased, evaluation-led rollout would also allow the evidence base to mature, enabling future analyses to explore longer-term outcomes, service utilisation and downstream economic effects with greater confidence.

Future research should prioritise longer-duration trials and real-world evaluations to better understand the durability of

cognitive and quality-of-life benefits associated with probiotic supplementation. In particular, further work is needed to examine adherence over time, differential effects across population subgroups and the relationship between short-term cognitive improvements and longer-term health and care outcomes. Embedding robust evaluation frameworks within any pilot programme would help strengthen the evidence base and inform future policy decisions.

By addressing identified risks through careful programme design and ongoing evaluation, the potential value of microbiome-modulating interventions can be assessed rigorously and responsibly. Such an approach supports proportionate, evidence-informed decisions about their role within future dementia prevention and care strategies, while remaining aligned with broader NHS sustainability and public health priorities.

# Appendices

# Appendices

## Appendix 1 - Systematic Review Search Strategy

Two investigators (Dr Harry Jarrett and Dr Ryan McNally) conducted systematic literature searches of three separate electronic databases, namely PubMed, Embase and PsychInfo. The searches were limited to articles published in the English language, filtered by “Randomised Controlled Trials” and adults. The searches were conducted up until the 21st May 2025 with no date limits. An example of the search strategy (in Medline) is below:

Set	Search Term	Results
1	(Probiotic or Probiotics or Probio).ab,ti.	181208
2	(Lactobacill* or Bifidobacter* or Lactococcus* or Saccharomyce or Pediococcus or Streptococcus or Lactic Acid Bacteria or L rhamnosus or L casei or L plantarum or L fermentum or L gasseri or B breve or B bifidum or B infantis or B subtilis or S thermophilus or S boulardii or E coli Nissle or B coagulans).ab,ti.	165814
3	(Prebiotic or Prebiotics or Prebio).ab,ti.	15319
4	(Fructooligosaccharides or Fructo-oligosaccharides or Galactooligosaccharides or Galacto-oligosaccharides or Transgalactooligosaccharides or Trans-galacto-oligosaccharides).ab,ti.	2976
5	(Synbiotic or Synbiotics or Symbiotic or Symbiotics or Psychobiotic or Postbiotic).ab,ti.	25769
6	1 or 2 or 3 or 4 or 5	235442
7	(Cognitive Function or Cognitive Functions or Cognition or Cognitions or Memory or Alzheimer* or Dementia* or "Cognitive Disorder" or "Cognitive Dysfunction" or "Cognitive Impairment" or MCI or Executive Function or Attention or Processing Speed or "Global Cognition" or MMSE or MoCA or "ADAS-Cog" or "Trail Making Test").ab,ti.	1366514
8	6 and 7	6359
9	Limit 8 to (english language and humans and "all adult (19 plus years)" and (randomized controlled trial or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial))	113

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## Appendix 2 - Meta-analysis Study Selection Protocol

The inclusion criteria were established following the Participants, Interventions, Comparisons, Outcomes and Study Design (PICOS) framework. Studies were excluded if (1) reported data could not be extracted; (2) the gut microbiome modulating intervention included another active component (e.g. dual intervention with another nutrient or lifestyle intervention); (3) the study design was unclear; and (4) the full text of the study was not found.

### PICOS Criteria for Inclusion and Exclusion of Studies

Parameter	Criteria
Population	Adults aged $\geq 18$ years, healthy and disease states
Intervention	Supplementation with gut microbiome modulating intervention, including pre, pro and syn-biotics only
Comparison	Placebo
Outcome	Changes in cognitive function, cognitive domains
Study Design	Randomised Controlled Trials

*PICOS= Population, intervention, comparison, outcome, and study design*

# Appendices

## Appendix 3 - Detailed Economic Modelling Protocol

We developed a cohort Markov model to estimate the cost-effectiveness of an NHS-funded probiotic supplementation programme for people living with dementia in the UK. The model compares standard care alone (control) with standard care plus a daily probiotic supplement (intervention) offered as a hypothetical national public-health programme.

The intervention arm assumes that the probiotic is offered for a 5-year policy window to all people with diagnosed dementia. Uptake ramps linearly from 50% of the alive cohort at roll-out to a plateau of 65% by year 2, after which coverage remains stable while the policy is active. A 12% annual discontinuation rate is applied to reflect real-world non-adherence, meaning roughly half of those who start supplementation are still taking it by year 5. Programme effects are assumed to be purely symptomatic: the probiotic does not alter disease progression or survival, but improves health-related quality of life ('QALYs') while individuals remain on therapy. We used the standard metric for cost-effectiveness – the incremental cost-effectiveness ratio (ICER) – which measures the extra cost per extra year of good-quality life gained.

The model structure and inputs were informed by previous similar work and relevant literature. We applied the usual NHS approach of discounting future costs and benefits at 3.5% per year (treating benefits gained in the future as slightly less valuable than benefits gained now). A key assumption in our model is the mapping of the change in baseline cognition (as measured by the MMSE, a dementia-specific cognition test) to changes in quality of life – previous research has indicated that the strength of this correlation is moderate. Hence, our assumption of how much a change in a person's MMSE score leads to an improvement in quality of life was highly conservative.

## Limitations and key uncertainties

The model is designed to be deliberately conservative and policy-focused but has several limitations:

- **Evidence base and effect durability:** The meta-analysis pools a relatively small number of short-term RCTs. Extrapolating average MMSE gains over a 5-year horizon assumes that benefits are maintained while individuals remain on therapy and do not attenuate; this may over- or under-estimate long-term impact.
- **Cognition–utility mapping:** Utilities are derived indirectly from MMSE changes using published cross-sectional/longitudinal relationships and a simple linear mapping within severity bands. EQ-5D has known limitations in dementia and the true cognition–utility relationship is uncertain, although we deliberately used modest slopes and wide sensitivity ranges.
- **Structural simplifications:** The model does not assume that probiotics reduce hospital admissions, delay care-home entry, or save unpaid carer time. Any such benefits would tend to reduce costs and increase QALYs, so current estimates likely understate potential value. Conversely, we do not include programme set-up, monitoring or adherence-support costs.
- **Generalisability and behaviour.** Uptake and adherence assumptions (50–65% uptake; 12% annual dropout) are based on judgement informed by general supplement adherence rather than direct evidence in dementia populations; real-world participation could be lower or more socially patterned.

These uncertainties are explored through sensitivity analyses, but residual structural uncertainty remains.

## Cost analysis and economic considerations

### 1. Estimation of costs and benefits

In the base-case analysis, the probiotic programme:

- Costs the system more overall than current care alone, because the NHS has to buy and distribute the probiotic and no cost savings are assumed
- Delivers more years of good-quality life for people with dementia, because their quality of life is assumed to be slightly better while they are on the supplement

In numbers, the probiotic programme increases total discounted costs by approximately £159m. This additional cost represents <1% of the total societal cost of dementia over this period (approximated at £229.9bn).

At the same time, the programme is assumed to yield an additionally 34,000 QALYs. This corresponds to an incremental cost-effectiveness ratio (ICER) of £4,702 per QALY gained, well below the commonly used willingness-to-pay range (£20,000–£30,000/QALY) that the NHS applies when assessing drugs and public health programmes for reimbursement.

The probiotic itself is costed at about £4.80 per person per month (around £57–58 per year). This is roughly £1.10 per week per person on the programme. At the level of the individual, the model suggests that this small weekly investment in the probiotic buys a modest but real improvement in quality of life each year - about 4 extra days of good-quality life per year. For every 1,000 people on the programme, this equates to over 4,000 additional “good-health” days annually.

Total nominal programme spend over five years is projected at around £170m, with annual costs rising from £27m in year 1 to approximately £38m in year 5 as uptake ramps up and the dementia population grows. Taken together, this represents <1% of the annual Public Health Grant allocated to local authorities in England, implying a modest budget impact at system level.

## 2. Potential savings to the NHS

Our model assumes that probiotics do not change healthcare use (for example, GP visits, hospital admissions, or use of other medicines).

This is conservative. In reality, if better cognition, mood or gut health leads to fewer crises, infections, falls or behavioural problems, then:

- There could be small but important reductions in NHS costs (e.g. fewer emergency attendances, less use of certain medicines);
- There may also be benefits for unpaid carers (less stress, easier daily care), and for social care in general.

Because we do not include these possible savings, the model likely under-estimates the full value of the programme to the NHS and to society.

On the other hand, we also do not model any extra NHS costs for programme administration (staff time to explain, prescribe, monitor). These are likely to be modest, especially if the probiotic is fitted into existing dementia reviews.

## 3. Sensitivity analyses

### We tested how sensitive the results are to changes in our assumptions:

- One-by-one checks: We changed one assumption at a time (for example: smaller probiotic effect, weaker link between cognition and quality of life, higher or lower probiotic price, different dropout rates). In every case, the cost per extra year of good-quality life remained below the NHS threshold (£20,000/QALY);

- Combined “what if” scenarios: We also ran simulations where many assumptions vary together, to mimic real-world uncertainty. In these simulations, most of the results still show the probiotic programme providing extra years of good-quality life at a cost that would typically be regarded as good value for money.

Overall, the programme appears robustly cost-effective: the conclusions do not change unless we make very extreme and unlikely assumptions.

## **4. Potential return on investment**

Using a standard valuation of £20,000 per QALY, the additional 33–34k QALYs generated by the programme correspond to approximately £674m of health value, compared with around £159m in incremental discounted costs. This implies a net “health surplus” of ~£516m and a benefit-cost ratio of roughly 4:1 (i.e. every £1 invested yields ~£4 in monetised health gains). At a higher valuation of £30,000/QALY, the implied benefit-cost ratio rises to around 6:1.

From a public-health budgeting standpoint, the programme therefore appears to offer a substantial return on investment, generating substantially more value in health gains than it costs to deliver.

# Appendices

## Appendix 4 - Characteristics of the studies included in the meta-analysis

Study (Author, Year)	Country	Population	Sample Size	Mean age	Intervention	Dose	Duration	Cognitive test
Asaoka (2022)	Japan	Older adults with subjective memory complaints	115	Active: 77; Placebo: 79	PRO	20 Billion CFU	24 weeks	MMSE
Freijy Probiotic Supp (2024)	Australia	Healthy adults	58	30.5	PRO	24 Billion CFU	8 weeks	One back memory
Freijy Prebiotic Diet (2024)	Australia	Healthy adults	55	40.1	PRE	NA	8 weeks	One back memory
Freijy Synbiotic (2024)	Australia	Healthy adults	59	38.3	SYN	>24 Billion CFU	8 weeks	One back memory
Kobayashi (2019)	Japan	Subjective memory complaints (50-80)	117	61.5	PRO	21 Billion CFU	12 weeks	MMSE
Sanborn- Cognitive healthy (2020)	USA	Healthy adults	42	64.5	PRO	20 Billion CFU	12 Weeks	NIH Toolbox Total Cognition Score
Sanborn- Cognitive impairment (2020)	USA	Participants with objective evidence of cognitive impairment (52-75 y)	43	64	PRO	20 billion CFU	12 Weeks	NIH Toolbox Total Cognition Score
Xiao (2020)	Japan	MCI (50-79 y)	79	61	PRO	2 billion CFU	16 weeks	RBANS
Hwang (2019)	Korea	MCI (Suspected)	100	68.6	PRO	10 Billion CFU	2 weeks	Computerized neurocognitive-function tests
Sakurai (2022)	Japan	Older adults with evidence of early memory deterioration	76	77	PRO	5 Billion CFU	12 weeks	Cognitrix- Visual Memory Test, Verbal Memory Test
Kim (2021)	Korea	Healthy free-living older adults (> 65 yrs)	63	71.4	PRO	1 Billion CFU	12 weeks	World Recall
Azuma (2023)	Japan	Healthy older adults	67	63.5	SYN	10 Billion CFU	12 weeks	Cognitrix
Ohsawa (2018)	Japan	MCI (Self identified forgetfulness)	60	58	PRO	NA	8 weeks	RBANS
Akbari (2016)	Iran	AD Patients	60	80	PRO	2 Billion CFU	12 weeks	MMSE
Shi (2022)	China	Healthy older adults	60	64	PRO	50 Billion CFU	8 weeks	RBANS
Agahi (2018)	Iran	AD Patients	48	80	PRO	3 Billion CFU	12 weeks	TYM
Fei (2023)	China	MCI	42	76	PRO	>40 Billion CFU	12 weeks	MMSE
Roman (2018)	Spain	Fibromyalgia patients	31	52	PRO	6 Million CFU	8 weeks	MMSE
Mehmandoust (2024)	Iran	AD patients	52	77	SYN	1 Billion CFU	12 weeks	MMSE
Grant 1bn CFU (2025)	USA	Anxiety patients- mild to moderate	58	39	PRO	1 Billion CFU	6 weeks	Sandia's Progressive Matrices
Grant 5bn CFU (2025)	USA	Anxiety patients- mild to moderate	58	39	PRO	5 Billion CFU	6 weeks	Sandia's Progressive Matrices
Wang (2022)	China	Temporal lobe epilepsy patients	70	60	PRO	20 Million CFU	12 weeks	Wechsler Memory Scale-Fourth Edition-
Sanborn (2022)	USA	Healthy middle aged and older aged adults	127	64	PRO	20 Billion CFU	12 weeks	NIHS Toolbox
Abe (2024)	Japan	Healthy elderly	61	67	PRE	5 grams (no CFU reported)	12 weeks	Cognitrix

Ahrén (2024)	Sweeden	Healthy elderly aged over 70 with low grade systemic inflammation	40	73	PRO	10 Billion CFU	4 weeks	Trail Making Test- B
Akhgarjand L. rhamnosus (2022)	Iran	Mild and moderate AD patients	60	67	PRO	2 Quadrillion CFU (10 x 15 cfu in one capsule 2 taken daily)	12 weeks	MMSE
Akhgarjand B. longum (2022)	Iran	Mild and moderate AD patients	60	67	PRO	2 Quadrillion CFU (10 x 15 cfu in one capsule 2 taken daily)	12 weeks	MMSE
Eastwood (2025)	UK	Healthy Older Adults	30	71	PRO	5 Billion CFU	8 weeks	The Rey Auditory Verbal Learning Task
Ruiz-Gonzalez (2024)	Spain	Healthy Older Adults	33	66	PRO	3.3 Billion CFU	10 weeks	MMSE
Ascone (2022)	Germany	Healthy adults aged 18-40	59	25	PRO	450 Billion CFU	4 weeks	Corsi block tapping task
Czajeczny (2023)	Poland	Healthy, young adult females-aged 19-31 yrs	38		PRO	4 Billion CFU total	6 weeks	Rey Auditory Verbal Learning Test
Mullish (2024)	England	Females (aged 18–40) diagnosed with IBS	56	32	PRO	25 Billion CFU	8 weeks	Modified Stroop word colour test
Chung 500 mg (2014)	Korea	Healthy older adults	10	65	PRO	No CFU stated just grams of extracted fermented milk in capsule	12 weeks	VLTA A20 Delayed recall
Chung 1000 mg (2014)	Korea	Healthy older adults	7	65	PRO	No CFU stated just grams of extracted fermented milk in capsule	12 weeks	VLTA A20 Delayed recall
Chung 2000 mg (2014)	Korea	Healthy older adults	9	65	PRO	No CFU stated just grams of extracted fermented milk in capsule	12 weeks	VLTA A20 Delayed recall
Onning (2024)	Ireland	Moderately stressed adults (21-52)	129	35	PRO	10 Billion CFU	12 weeks	Word Recall
Kelly (2017)	Ireland	Young healthy male adults (aged 20-33 years)	29	25	PRO	1 Billion CFU	8 weeks	Paired Associate Learning
Allen (2016)	Ireland	Young healthy male adults (aged 20-33 years)	22	22	PRO	1 Billion CFU	4 weeks	Paired Associate Learning
Cannavale (2023)	USA	Young healthy adults (25-45 years)	26	33	PRO	25-30 Billion CFU	4 weeks	Hippocampal-dependent relation memory- Object-Location Binding
Nagasaki (2019)	Japan	Healthy mid-old adults with self-reported memory impairment (50-69 years)	56	58	PRO	5 Billion CFU	12 weeks	Cognitrix

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## Appendix 5 - Economic Modelling Inputs

Variable	Value	Lower - upper range (sensitivity analysis)	Sources	Commentary
Excess annual mortality - mild	0.00	-	Mukadam et al 2024	Excess mortality above age-specific mortality. Original estimates from Brookmeyer et al
Excess annual mortality - moderate	0.11	0.07 - 0.15	Mukadam et al 2024	
Excess annual mortality - severe	0.11	0.07 - 0.15	Mukadam et al 2024	
Discount Rate	3.5%	1.5% - 3.5%	NICE	Standard discounting rate for future costs and utility gains as per NICE guidance
Time horizon	5 years	-	-	Reasonable timeframe for a public health programme roll-out
Net prevalence growth rate	2.3% p.a.	1.5% - 3.0%	-	Annual increase in total number of people living with dementia
Annual costs per person - mild	£28,700	£18,568 - £40,997	CF/Alzheimer's Society: The economic impact of dementia	Total costs of dementia including healthcare, social care, unpaid care, economic costs and QoL costs (e.g. energy costs, scams, police callouts)
Annual costs per person - moderate	£42,900	£27,755 - £61,281		
Annual costs per person - severe	£80,600	£52,146 - £115,134		
Annual cost inflation - mild	2.8%	1.8% - 3.8%		
Annual cost inflation - moderate	2.2%	1.2% - 3.2%	-	Annual cost inflation factor as per CF study
Annual cost inflation - severe	2.8%	1.8% - 3.8%	-	

Variable	Value	Lower - upper range (sensitivity analysis)	Sources	Commentary
Starting cohort - mild	488,000	-	CF/Alzheimer's Society: The economic impact of dementia	Estimated prevalence split, UK
Starting cohort - moderate	374,000	-		
Starting cohort - severe	130,000	-		
Starting cohort age - mild	80	77 - 83	Assumption	Assumed lower than new diagnosis due to mid-stage convention
Starting cohort age - moderate	85	82 - 88	Assumption	
Starting cohort age - severe	87	84 - 90	Assumption	
New diagnosis cohorts - mild	47.5%	41.9% - 53.1%	Petersen et al 2021 (DANDEM)	% of newly diagnosed cases that are at each stage
New diagnosis cohorts - moderate	43.5%	37.9% - 49.1%	Petersen et al 2021 (DANDEM)	
New diagnosis cohorts - severe	9.0%	5.8% - 12.2%	Petersen et al 2021 (DANDEM)	
New diagnosis cohort age - mild	78	75 - 81	Petersen et al 2021 (DANDEM)	Modelled on assumed average age of mild patients at diagnosis - 78. Other ages extrapolated from assumed transition probabilities and average duration in stage
New diagnosis age - moderate	83	81 - 86	Assumption	
New diagnosis age - severe	85	82 - 88	Assumption	

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## Appendix 6 - Detailed Findings of the Economic Modelling Analysis

The model follows a prevalent UK dementia cohort plus incident cases over five annual cycles (time horizon 5 years), with 1-year cycle length and a 3.5% annual discount rate applied to both costs and QALYs in line with NICE guidance. Health states reflect dementia severity: mild, moderate, severe and death. Stage-specific prevalence, ages, transition probabilities (mild→moderate, moderate→severe), and excess mortality hazards above age-specific life-table risks were drawn from Mukadam et al. (2024) and related natural-history work by Brookmeyer and colleagues. A net 2.3% annual increase in dementia prevalence was calibrated to match recent UK burden estimates.

Treatment benefit in cognition was estimated via a random-effects meta-analysis of placebo-controlled RCTs of probiotic supplementation in people with dementia, stratified by baseline severity and using MMSE as the common outcome. Pooled mean differences were 2.90 points for mild dementia, 4.03 for moderate dementia and 2.37 for severe dementia; because the severe-stage estimate was not statistically significant, a zero effect was assumed for severe dementia in the base case, with the full uncertainty interval explored in sensitivity analyses.

These MMSE gains were mapped to EQ-5D-compatible utility changes using conservative slopes derived from published datasets linking cognition and utilities in dementia (Keetharuth 2022, Hussain 2022, Rombach 2021, Martin 2019, Wolfs 2007).

Stage-specific baseline utilities were taken from Anderson et al. (2018) (0.71 mild, 0.64 moderate, 0.38 severe). Stage-specific annual costs were taken from the “Economic impact of dementia” report (CF/Alzheimer’s Society), capturing health-care, social-care, unpaid-care and wider societal costs (£28,700 mild, £42,900 moderate, £80,600 severe in the base year), with stage-specific inflation factors applied over time. The probiotic price in the base case was set at £4.80 per month (£57.60 per year), consistent with a discounted NHS procurement price and validated with industry experts.

Deterministic one-way sensitivity analyses show that the ICER is most sensitive to: (i) the assumed price of the probiotic and (ii) the mapping from MMSE gains to utilities ( $\alpha$ -slope) and, to a lesser extent, the underlying MMSE effect sizes. Varying these parameters across conservative ranges keeps the ICER comfortably below £10,000/QALY in all explored scenarios.

A dedicated price-threshold analysis, varying only the probiotic price while holding other parameters at conservative values, indicates that in the “worst-case” scenario the ICER would only breach £20,000/QALY at a monthly cost above approximately £7.80—around 60% higher than the base-case price of £4.80/month. This suggests substantial headroom for price variation without compromising cost-effectiveness.

Probabilistic sensitivity analysis (1,000 Monte Carlo simulations) further supports the robustness of the finding. With price held constant at £4.80/month, the mean ICER across simulations is £3,912/QALY (95% percentile range ~£2,249–£6,815/QALY). When price is also allowed to vary within the prespecified range, the mean ICER rises to £4,895/QALY (95% range ~£1,617–£10,320/QALY), and virtually all simulations remain below the £20,000/QALY threshold.

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