

CURRENT ALZHEIMER RESEARCH

TITLE PAGE

Title: Systematic review investigating multi-disciplinary team approaches to screening and early diagnosis of dementia in primary care – what are the positive and negative effects and who should deliver it?

Running Title: Screening and early diagnosis of dementia

Authors: Smith TO, Cross J, Poland F, Clay F, Brookes A, Maidment I, Penhale B, Laidlaw K, Fox C

Affiliations

Dr Toby Smith - University Lecturer, School of Health Sciences, University of East Anglia, Norwich, UK.

Dr Jane Cross - Senior Lecturer, School of Health Sciences, University of East Anglia, Norwich, UK

Prof Fiona Poland - Professor of Social research Methodologies, School of Health Sciences, University of East Anglia, Norwich, UK

Dr Felix Clay - Core Psychiatry Trainee, Peterborough City Hospital, Peterborough, UK

Abbey Brookes – Physiotherapy Student - School of Health Sciences, University of East Anglia, Norwich, UK.

Dr Ian Maidment - Senior Lecturer, School of Life and Health Sciences, ARCHA, Aston University, Birmingham, UK

Dr Bridget Penhale - Reader in Mental Health, School of Health Sciences, University of East Anglia, Norwich, UK.

Prof Ken Laidlaw - Professor of Clinical Psychology, Norwich Medical School, University of East Anglia, Norwich, UK.

Prof Chris Fox - Professor of Clinical Psychiatry, Norwich Medical School, University of East Anglia, Norwich, UK.

Corresponding Author: Professor Chris Fox, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TK. Email: chris.fox@uea.ac.uk; Telephone: 044 (0)1603 593583; Fax: 044 (0)1603 593316

ABSTRACT

Background: Primary care services frequently provide the initial contact between people with dementia and health service providers. Early diagnosis and screening programmes have been suggested as a possible strategy to improve the identification of such individuals and treatment and planning health and social care support.

Objective: To determine what early diagnostic and screening programmes have been adopted in primary care practice, to explore who should deliver these and to determine the possible positive and negative effects of an early diagnostic and screening programme for people with dementia in primary care.

Methods: A systematic review of the literature was undertaken using published and unpublished research databases. All papers answering our research objectives were included. A narrative analysis of the literature was undertaken, with the CASP tools used appropriately to assess study quality.

Results: Thirty-three papers were identified of moderate to high quality. The limited therapeutic options for those diagnosed with dementia means that even if such a programme were instigated, the clinical value remains questionable. Furthermore accuracy of the diagnosis remains difficult to assess due to poor evidence and this raises questions regarding whether people could be over- or under-diagnosed. Given the negative social and psychological consequences of such a diagnosis, this could be devastating for individuals.

Conclusions: Early diagnostic and screening programme have not been widely adopted into primary care. Until there is rigorous evidence assessing the clinical and cost-effectiveness of such programmes, there remains insufficient evidence to support the adoption of these programmes in practice.

Keywords: Diagnostic; Population screening; cognitive impairment; experiences; general practice; community services

INTRODUCTION

Dementia is a growing issue for society. An estimated 47.7 million people globally suffer from Alzheimer's disease (AD), the most common dementia subtype [1]. Alzheimer's disease pathology begins long before cognitive and functional impairments are noticed thus early intervention might delay symptom onset and progression. If no breakthrough can be made to prevent the disease or delay its onset, the number of people with dementia is anticipated to reach 135 million by 2050 [2].

By 2030 it is estimated that the global cost of caring for people living with dementia could be US\$1.2 trillion or more [3]. By 2047, assuming a curvilinear association between age and dementia risk, a 2-year delay in onset would reduce population incidence by 22% [3] resulting in 25 million fewer cases worldwide [4,5]. In addition to these economic impacts, there is increasing evidence linking modifiable risk factors, such as diabetes mellitus, hypertension, obesity, physical inactivity, depression, smoking, and educational attainment with dementia incidence [6].

Currently early diagnosis, information, advance care planning, cognitive stimulation therapy, management of neuropsychiatric symptoms, strategies for family carers, cholinesterase inhibitors and memantine in dementia and changes in attitudes, including highlighting personhood and living well with dementia, have made notable strides forward but there is, as yet, no cure, effective preventative intervention nor disease modifying treatment for the common dementias.

The diagnosis of dementia is advancing in terms of accuracy, but there are still major technical and ethical issues for implementation [7]. Primary care is the first access point for many people with memory concerns but there may not be the resources or skill-set to manage the complex care needs of this of every increasing number of patients.

A recent systematic review examined the wider attitudes and preferences of the general public, health care professionals, people with dementia and their carers towards screening for dementia [8]. In their review, Martin et al [8] did not aim to specifically examine what diagnostic practices were, who should deliver 'early diagnosis of dementia programmes' in primary care and what the potential positive/negative effects of such interventions might be. The intention of this systematic review is to address these specific questions.

MATERIALS AND METHODS

A systematic review methodology was undertaken according to established methods of systematic reviewing [9] and reported in accordance with the PRISMA reporting statement [10].

Aim

The aims of this review were to determine:

- a) What the clinical practices are in early diagnosis and screening approaches for dementia in primary care.
- b) Who should deliver early diagnostic and screening programmes for dementia in primary care?
- c) What are the potential positive and negative effects of early diagnosis or screening programmes for dementia in primary care?

Search Strategy

The primary search strategy was conducted on the electronic databases MEDLINE, AMED, EMBASE, PubMed using the search strategy terms and Boolean operators as presented in **Table 1**. In addition, a secondary search of the grey literature and trial registries was conducted including the databases: OpenGrey, WHO International Clinical Trials Registry Platform, Current Controlled Trials, UKCRN Portfolio Database, National Technical Information Service and the UK National Research Register Archive.

The search was undertaken from each database's inception to 5th October 2015. A review of the potentially included papers' reference lists and previous review articles was undertaken to identify any additional studies not identified by the primary search.

Eligibility criteria

All papers presenting data on the screening or diagnosis of people for dementia, conducted in primary (community) care or family practice, were eligible for inclusion in this review. Since we were particularly interested in the diagnosis of older people with dementia, we excluded studies where 80% or more of their cohort consisted of people aged less than 65 years. We included papers reporting all types of dementia, regardless of the

form of primary care screening/diagnostic services, age, quality or language of publication. All study designs were considered for inclusion.

Selection of Studies and Data Extraction

Two review authors (TS and FC) independently reviewed the titles and abstracts from all search results based on the eligibility criteria. The full texts from all potentially eligible papers were ordered and re-reviewed against the eligibility criteria. All papers adhering to the criteria on assessment of full texts were included in the review. In case of disagreement at any stage of the selection of studies, a third author acted as adjudicator (CF).

All key study data was extracted onto a pre-defined data extraction sheet. Three review authors (CF, AB, TS) performed this task independently. Data extracted included: study design; patient population characteristics such as age, gender, cognitive impairment, co-morbidities to dementia, age at diagnosis, duration from symptom onset to diagnosis; primary care clinician involved in diagnosis and screening; perceived positive and negative effects of screening procedure in primary care, and perceptions of primary care early diagnosis and screening programmes of cognitive impairment delivered in the community and primary care settings.

Assessment of Study Quality

The quality of the identified studies was assessed using the CASP critical appraisal tools [11]. Studies were classified as high, moderate and low quality using the threshold values of low (0-5 points), moderate (6-8 points) and high (9-10 points). The relevant CASP tool was selected to reflect the study design. Any disagreements in study identification, data extraction or appraisal were resolved through discussion between the three reviewers (FC, AB, TS), or adjudication with a fourth reviewer (CF).

Data Analysis

The purpose of this review was to determine reported clinical practice in primary care for early diagnosis and screening programmes for dementia, including who should/does undertake this and what may be the positive and negative effects of this practice. These later parameters are based on the opinions and attitudes of all stakeholders including patients and carers, primary and secondary care clinicians, health care commissioners and academics. As the intention of this analysis was to describe practice and both attitudes and opinions, a descriptive analysis was undertaken with a narrative review rather than a pooled analysis of results. Frequency of responses and attitudes towards early diagnosis or screening and difference between health care clinicians and patient attitudes (where appropriate) to these diagnostic pathways were recorded and presented narratively.

RESULTS

Search Results

Figure 1 presents a summary of the search results. In total, from 215 citations, 121 were screened after removal of duplicates. From these, 66 citations were excluded since it was clear from both their titles and abstracts that they did not meet the eligibility criteria. The full-text of 55 were reviewed, with 22 studies excluded on full-text review. Of these four were not based in a primary care/community setting, five were not related to early diagnosis of dementia, and 13 did not provide data answering one of more of the *a priori* research questions. The remaining 33 studies were identified as meeting the eligibility criteria and were included in the review. The study designs and characteristics of the included papers are presented in **Table 2**.

Quality Assessment

Twenty-six papers presented original research findings and were critically appraised for risk of bias. Seven papers were commentary review papers and therefore not assessed using a critical appraisal tool. A summary of the quality of the included papers is presented in **Table 3**. This illustrates that the evidence was of moderate to high quality. With the exception of Perry [12], an RCT, the remaining studies used various methods: qualitative methods were used to assess the attitudes and perceptions of primary care clinicians to early diagnosis; surveys to assess current practices in early diagnosis and implementation studies of early and supported dementia diagnosis or screening programmes. Recurrent strengths in the literature included the clear identification of participant recruitment processes (97%), clear data collection processes (94%), sufficient follow-up of participants with minimal attrition (94%), and assessing outcomes over a sufficient follow-up interval to provide valuable data (97%). Recurrent limitations were not controlling or accounting for possible factors, which could have confounded outcomes (15%) and not presenting quantitative data (when indicated) with confidence intervals to gain an indication of the precision of the finding (18%).

Clinical practices of primary care early diagnosis or screening for dementia

There has been little literature exploring what clinical practices are for the early diagnosis or screening for dementia in primary care. Four studies explored screening practices in primary care for early diagnosis of dementia

[13,14,15,16]. There was considerable heterogeneity in how such screening programmes were delivered. Diagnostic practices were based on either opportunistic or formal (sub-populations) until the '75 years and over check' in the United Kingdom was introduced [13]. Banerjee et al [17] paper reported an early identification/diagnostic intervention specifically designed to provide early assessment and management of people with dementia largely delivered in their own homes in South London. Most recently Russell et al [16] reported the results of using Read codes to identify, people who may have dementia or be at risk of dementia, then to assess these individuals as part of a Quality and Outcomes Framework (QOF) review.

Whilst formal screening was supported in Iliffe et al's [13] review of UK GP attitudes in a workshop on dementia diagnosis, such a potential programme was considered as unfeasible by other respondents due to the reported prevalence of dementia and large number of potential patients. The time and resources required were considered too great to make a national screening programme feasible [13]. However opportunistic screening was considered inappropriate given the time it takes to execute assessments using tools such as Mini-Mental State Examination (MMSE) [18] and Abbreviated Mental Test Score (AMTS) [19] which could not be included in a GP consultation in addition to the original reason for the GP appointment [13].

In contrast Manthorpe et al [15] presented findings from 24 workshops across 21 UK cities on community healthcare professionals' role in early dementia diagnosis. They reported agreement that opportunistic screening was both appropriate and possible suggesting that as part of routine consultations professionals could detect 'cues' of cognitive impairment such as behaviour change, reduced self-care and agitation.

The exact timing of when to investigate early dementia was explored by Hansen et al [13] in a qualitative study of Australian GPs practice in dementia assessment. The two most commonly adopted times were when (1) patients or their family members present to the GP complaining of declining memory, reduced emotional control, change in social behaviour or (2) where there is a decline in thinking and planning activities. Hansen et al [13] acknowledged that diagnosis could be made when the GP observes 'early pointers' which include forgetting appointments or medications, social withdrawal and decline in self-care. However, it was acknowledged that these can be difficult to detect or may be interpreted incorrectly, with GP's attributing such symptoms to tiredness, old age or depression [13]. Boise et al [20] highlighted, in their findings from 18 focus groups of 78 GPs, that family members and carers frequently provide the contextual information about the patient's behaviour that would

provide the trigger to further diagnostic investigations. Without this family or carer input the early diagnosis of dementia in primary care was considered challenging, with the subtlety of dementia recognition in the early phases a considerable barrier to initial recognition which is further intensified by a patient's denial or refusal to accept what is happening.

Holsinger et al [21] presented their findings from the Dementia Screening and Perceived Harms (SAPH) questionnaire in two older adult populations in primary care. They reported that 86% of the 345 patients approached were happy to be screened, and that it was feasible to incorporate a screening programme into clinical practice with minimal disruption. Fowler et al [22] examined 554 community-dwelling individuals aged 65 years and older in Indiana for their willingness to be screened for dementia. They found that 90% of participants agreed to screening, suggesting its adoption is positively viewed. However, more recently Fowler et al [23] report only 63% acceptance in a cohort of 400 people when the Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC) questionnaire was used as the screening tool. However no studies have reported how this or other potential screening tools are used in non-research driven clinical practice.

Banerjee et al's [17] Croydon Memory Service Model was assessed through 290 consecutive referrals over a six-month period. They reported that this multi-disciplinary intervention successfully engaged with minority ethnic groups, younger adults (17% of referrals to under 65 years old), and successfully decreased behaviour disturbance (assessed using the Neuropsychiatric Inventory) and increased quality of life (assessed using the self-rated DEMQOL or carer-rated DEMQOL-Proxy) [24] for those who used the service. However this follow-up data was based on the responses of 141 participants and therefore may provide biased results from a self-selecting sample. Nonetheless the refusal rate for dementia assessment was only five percent, suggesting acceptance as demonstrated in other studies such as Holsinger et al [21] and Fowler et al [22,23].

Rather than developing a new service or screening programme, Russell et al [16] reported using Read codes to identify individuals at risk of dementia on primary care patient lists. They recruited 23 general practices from 19 areas of London with a total practice population of 179,312 with 19,562 patients aged 65 years or older. This intervention, which cost each practice an average of 4.7 hours of administration time, increased the number of identified people with dementia from 1007 to 1139 people. This represents an increase in identification rates of

8.8% ($p=0.004$) with a purposeful strategy in a population who may not have attended their GP clinic for an alternative reason.

Who should provide early diagnosis of dementia in primary care?

Nine studies were identified which specifically explored 'who' should deliver screening programmes for people with dementia [12,17,25,26,27,28,29,30,31].

Iracleous et al's [25] survey of 249 GPs in Canada reported overwhelming agreement that cognitive impairment assessment was important in primary care (89% agreed); 92% further agreed that screening should not be left to specialist services, with GPs taking a leading role in cognitive screening.

Manthorpe and Iliffe [26] assessed perceived difference in confidence of diagnosis between community mental health nurses (CMHN), community nurses and practice nurses. They reported that CMHNs were most confident about diagnosing dementia (87%) compared to 46% of community nurses and 42% of nurse practitioners. However, when asked about confidence of diagnosing people who presented with mild cognitive impairment, only 11% of CMHNs felt confident of their diagnostic skills, although this was greater than community nurses (3%) and practice nurses (8%). In their workshops on screening for dementia, Manthorpe et al [13] identified an array of professional groups who may appropriately undertake screening for cognitive impairment. These included practice nurses, health visitors, community or district nurses, community psychiatric nurses, GPs, other (unspecified) nurse, social workers, memory clinic staff and lay person/voluntary organisations. This multi-disciplinary approach was supported in Banerjee et al's [17] Croydon Memory Service Model, which was based on a team of physicians and nurses training in dementia assessment and care, working as a "core generic team".

There appeared consensus, within the reviewed European literature, that general practitioners and family physicians were confident about their capability to identify cases of people with dementia with 81% of 113 GPs in the East of England reporting being confident [27]. However Cahill et al [28] report that GPs in Ireland may be afraid to diagnose dementia and initiate treatment, had limited time to undertake a thorough assessment and therefore felt that routine GP consultations might not be the optimal place to undertake such an assessment. This study of 300 GPs in Ireland also highlighted a lack of GP education on dementia diagnosis in both undergraduate

and postgraduate education. They also highlighted that in rural primary care services, difficulties in accessing computer tomography and magnetic resonance imaging facilities provided a key obstacle to dementia diagnosis [28]. From a worldwide perspective, Turner et al [30] reported that only 50% of their cohort of 127 GPs had sufficient basic knowledge to make an early detection of diagnosis and therefore training may be a major challenge when considering who should undertake this screening.

Education and training in primary care services for dementia diagnosis has been investigated in two studies. Perry [12] reported a cluster randomised controlled trial of usual care versus education through a dementia training programme for family physicians and practice nurses in the Netherlands. The intervention consisted of two workshops, individual coaching, Internet support and a computerised decision support system. They concluded that there was a significant difference in the number of assessments of potential patients (92% versus 32%) and diagnoses made in routine primary care compared to practices that did not have access to the dementia training programme (49% versus 15%; $p < 0.001$). There was also greater adherence to national dementia management guidelines in the dementia training programme clusters (74% versus 42%). Secondly, Pond et al [29] reported the reliability of dementia diagnosis following a 15 minute face-to-face training intervention with a GP academic fellow with a special interest in geriatric dementia. They reported no significant improvement in the reliability of dementia diagnosis during a six month period hence raising questions about the value of this brief intervention. This contrast in results may well reflect the differing intensity and levels of training offered.

Martin et al [31] uniquely, explored the issues around dementia screening with patients *and* the public. In their interviews patients largely felt that clinicians should be qualified to undertake the assessment and therefore training was critically important. When asked about which professional group should undertake these assessments there was limited agreement with participants suggesting that it was the specialist training that was important. This could be social services, or health care professional such as a GP or nurse. Some respondents favoured this being a GP proposing that the family GP knows the individuals and that this familiarity could be beneficial. They suggested that this may make the acceptance of the result easier if there is trust and a strong rapport between the patient and GP. In contrast, others argued that this shouldn't be the GP as they have insufficient time to do such an important assessment and may not be adequately skilled [31].

What are the positive and negative effects of early diagnosis in primary care?

Positive Effects

Six positive effects of primary care screening and early diagnosis of dementia included improved long-term outcomes, increased detection, increased ability to plan; better psychological adjustment; avoidance of institutionalisation and income generation.

Improved long and shorter-term outcomes: Three papers [17,25,30] provided evidence of improved long-term outcomes. Nationally instigated, improved mechanisms aimed to improve rates of diagnosis and capture all rather than some of the patients with cognitive impairment, could increase their long-term outcome if treatment interventions develop and progress. However, a survey of 249 GPs in Canada suggested 35% were undecided whether dementia screening would improve outcomes for patients in primary care [25]. Banerjee et al [17]'s findings of the Croydon Memory Service Model provided favourable findings for the adoption of a multi-disciplinary team memory service delivered in people's homes. They reported a significant difference in reduced behaviour disturbance and improved quality of life for individuals who were assessed as part of this service, during their six month follow-up period [17].

Increased detection: Three papers indicated that early dementia interventions and screening can increase the levels of detection of people with dementia, and are therefore effective [32,33,34]. Iliffe et al [33] reported that in their cohort of 139 patients screened in primary care in the London area, 99% of procedures (138/139) were undertaken and reported electronically after a 'pop-up' was used as a reminder to screen, with significantly more patients identified through this screening programme than normal clinical practice ($P \leq 0.01$). These findings reflect earlier reporting from a study of 659 individuals in New England [34].

Increased planning: Seven papers [13,31,35,36,37,38,39] describe the importance of planning health and social care provision before cognitive impairment has a significant impact on an individual's health, well-being and independence. It is proposed that this allows patients and families to be introduced early to agencies, which can improve quality of life and reduce risk of crises [37,38]. Early education for the patient and their family could avert crisis events when a person with dementia becomes critically unwell, which can be costly and distressing for them and for their family and carers [35,39].

Psychological adjustment: One paper explored the possibility that an early diagnosis of dementia might reduce psychological distress for individuals and their family or carers [13]. An early diagnosis may provide more time for patients and families to come to terms with the diagnosis and psychologically adjust [13]. This could be considered a significant advantage, particularly in improving quality of life for the individuals concerned.

Avoidance of institutionalisation: This potential advantage of screening and early diagnosis was discussed in five papers [13,17,35,36,40] which describe how it may facilitate planning provision of in-home support to reduce institutionalisation, increase independence and wellbeing of patients and support for families and carers [13,35]. This may also have a significant benefit on the quality of life for people with dementia and their carers [35]. Banerjee and Wittenberg [40] performed a cost-effectiveness analysis using the data from the Croydon Memory Service Model [17]. They reported that whilst such a new service would cost approximately £220 million extra per year nationally in England, the estimated saving of 10% of care home admissions could be prevented by Year 10, saving £120 million in social care costs and £125 million in private expenditure (patient and family/carer). This was therefore deemed as a potentially cost-effective intervention on the costs associated with institutionalisation alone [17].

Income generation: The idea that population screening might be an economical model for private health providers was suggested in one paper [36]. Whilst negative effects of early detection and screening may include costs associated with such programmes and continuing support for those who are diagnosed with cognitive impairment, for private health services this may create a new market. Therefore primary care screening provided by social enterprises or private health providers, given the high prevalence of dementia, could be an economically viable market, which has previously been under-represented [36].

Negative Effects

Eight negative effects to adoption of primary care screening and early diagnosis for dementia were identified from the evidence. These included over-diagnosis with poor prognostic value, insufficient evidence, a dearth of treatment options, social consequences, psychological consequences, costs associated; and limited service capacity to respond.

Misdiagnosis: Seven papers [13,30,35,36,37,41,42] discuss how early dementia with mild cognitive impairment could be diagnosed, which then however doesn't become established as a true dementia. This could lead to undue anxiety and 'scare mongering' about the patient's future and increased anxiety for the patient [35] and their family, as well as unnecessary service provision and lifestyle changes pre-dementia. Early diagnostic screening by imaging will detect only catastrophic changes especially for those aged 80 years and older and therefore risk cannot really be fully evaluated, particularly for those with cerebral co-morbidities [36]. There is currently insufficient evidence to support a specific screening measure or diagnostic test with acceptable accuracy for early dementia in primary care [41]. Beach et al [42] reported that the diagnosis of dementia sensitivity values ranged from 71% to 87%, but specificity values ranged from 44% to 71%; this provides further questions regarding a high misdiagnosis rate for early diagnosis of dementia.

Prognostic value: The prognostic value of dementia screening has been questioned in three papers [31,36,37], pointing out that whilst diagnosis is valuable, prognosis is then needed by patients and families to become meaningful. Thus it could be argued that diagnosis is not a valuable addition to healthcare provision without further evidence about how this can usefully inform people's futures.

Insufficient evidence-base: There is a paucity of research from intervention trials to support the provision of early diagnosis of dementia [13,31,36,37,41,42,43,44] and no strong evidence for accurate diagnoses of dementia in early phases [35,36,41,45]. Patients and the public also expressed concerns, stating that they thought it was critically important to establish the accuracy of the test before it should be used in clinical practice [31]. There is also no strong evidence to support the benefit of early diagnosis [42], a view supported by the UK national screening committee who highlighted this is as problematic, particularly given the absence of diagnostic screening criteria [45]. There is, therefore, insufficient evidence to support the adoption of early detection over later diagnosis [45].

Ineffective treatment: The lack of treatment options is a particular disadvantage of early diagnosis of dementia [31,35,36,37, 41,6]. Apart from symptomatic treatments there are currently no effective treatments for this population and therefore early diagnosis may raise fears, without any effective treatment options [35,36]. This means such a diagnosis could therefore be perceived as a potential 'death sentence', with potential long-term

negative psychological implications for individuals [31]. Furthermore, with the recognised possibility of over diagnosis, the NHS and social care sectors may not be able to afford to provide additional support to all individuals, given such potential high numbers of positively screened people.

Social consequences: The implications for wider society and the relationship between society and the patient were considered important negative effects in four papers [13,31,35,46,47]. It is possible that the results of the screening could affect employment status and options or health insurance and life insurance premiums, which may have social consequences for individuals and their families [35]. There could be stigma related to a diagnosis of dementia, which could then create social isolation and a loss of independence [31,35,46,47]. This may also affect or alter the social networks the person has, with potentially further negative social and psychological consequences.

Psychological consequences: Three papers explored potential psychological consequences of an early diagnosis of dementia [13,35,46,47] suggesting those affected could develop anxiety and depressive symptoms following the diagnosis with concerns regarding their future. The social consequences (stigma) of such a diagnosis may also cause social isolation and even greater anxiety and depression, which might develop further or spiral [13,34,46,47].

Financial Implications: The economic costs associated with providing dementia, screening programmes at a population-level, and early diagnosis of dementia for the public, were presented in six papers [13,31,35,36,40,41]. Given the high prevalence of cognitive impairment and dementia in the population, some authors have questioned how cost-effective such assessments would be in current health services worldwide [31]. Given the paucity of cost-effectiveness literature, there is a perception that this might not be value for money in the National Health Service [35]. However, Banerjee and Wittenberg's [40] analysis refuted this as highlighted above. Furthermore, if there is an increase in the number of people diagnosed, support and care will be required for these people, potentially at an earlier time than those diagnosed later, which would have further cost-implications in relation to the overall management for the population, and this may or may not be cost-effective [13,36]. There is therefore currently insufficient evidence that a screening programme or early diagnosis of dementia can be cost-effective in primary care [40].

Service capacity: Concerns regarding the practicalities of providing an early diagnosis in dementia were presented by Jacinto et al [38] and Iliffe et al [13] and currently primary care services are under pressure due to the number of patients seen within routine practice. Given the growing ageing population, the literature suggested that screening for cognitive impairment in primary care could only be delivered if economically incentivised. Additionally, some authors have questioned whether GPs and primary care nurses have the skills to be able to diagnose cognitive impairment in early screening. This would need to be addressed, with associated costs in training and education across the UK, to effectively provide this service. In Brazil for example, only 50% of GPs were reported to have the knowledge to apply early dementia screening tests. This could therefore be a major limitation, leading to worldwide problems in implementation [38]. However Iliffe et al [13] suggest that an early diagnosis screening programme or encouragement to diagnose people early in primary care may provide the impetus to improve knowledge about dementia diagnosis, so providing an opportunity to increase the relevant skills.

DISCUSSION

The findings of this review indicate that there is limited empirical research regarding the feasibility and usefulness of a screening programme and early diagnosis assessments within primary care. A significant proportion of the current literature on early screening programmes is based on healthcare professionals and patients views which although providing valid and interesting perceptions do not address the effect on clinical outcomes. Furthermore, given the poor evidence-base underpinning diagnostic accuracy, issues remain whether people could be over- or under-diagnosed. Until there is further evidence for the clinical and cost-effectiveness of early diagnosis and screening and until appropriate training and support for health care professionals is developed to implement such programmes, early diagnosis through screening is not an evidence-based intervention for current community care systems.

A major theoretical limitation to implementing an early diagnosis and screening programme for diagnosis in primary care concerns which healthcare professionals should take responsibility for this. Given the large number of patients who would need to be assessed in an ageing population, all healthcare professionals should take responsibility, screening and assessing opportunistically. Given that 80% of the population receive a primary care

appointment each year [48], such a strategy would appear realistic and achievable, if the assessment procedure could be undertaken within the constraints of a conventional primary care consultation. However, previous authors have suggested that those with moderate cognitive impairment consult their primary care physicians less frequently than those with no or mild cognitive impairment [49]. Accordingly such opportunistic strategies could fail to include a large number of individuals in particular need. Furthermore, this may be inappropriate given that early indications of cognitive decline can be more subtle changes in behaviour, memory and character, which are difficult to detect during a short consultation Martin et al [8]. Additionally there is often a reliance on reports from other family members, who may be less likely to mention this unless they had sought a consultation regarding dementia screening [31].

The need for training and educational support has also been highlighted as a recurrent argument against opportunistic diagnosis approaches, with authors such as Perry [12] and Manthorpe and Iliffe [26] suggesting that healthcare professionals in primary care need specific training in assessment approaches. Such a requirement raises issues of training costs and support, particularly for a nationwide diagnostic programme. Whilst a focus on specialist community nurses and psychiatric services may be a more realistic approach given their specialist skills, ensuring there is universal coverage and referral pathways to such services for all may be a logistical and financial challenge which may not be attainable in many health services.

The literature in this review highlighted the psychological and social implications following a diagnosis of dementia. There is suggestion that this may be beneficial to facilitate the early planning of care support and avoidance of 'crises' when the cognitive impairment starts to have a greater impact on inadequate family or carer support. Whilst in contrast the psychosocial implications, such as fear around loss of insurance, increased private health care premiums, loss of current employment and future employment opportunities, as well as relationship and family tensions which may culminate in social isolation and stigmatisation within wider society, have been widely reported within the literature [50,51,52]. Improved awareness of the consequence of mild cognitive impairment would appear an important precursor to prepare individuals before being screened with better information for family members, friends, employers and the government and public agencies is also required. Therefore, whilst implementation of early diagnostic and screening programmes may appear to only be important to primary care providers, in reality, this has far greater consequences for both wider sections of the public sector and society in general.

Given these challenges it is not surprising that at present screening programmes and early diagnosis are largely limited to research programmes and investigational rather than routine practice. The evidence underpinning the adoption of screening programmes in small, regional-population based cohorts, which are easily controlled, provides an indication of the potential for screening implementation [21,22,23]. However, it is difficult to generalise the findings from these to a national-level given the variations in population characteristics and difficulties in managing macro and meso-level system change. Such studies should only be considered once the evidence concerning the diagnostic test accuracy of screening tools, and the cost-effectiveness of such programmes at a national level have been studied and modelled.

CONCLUSIONS

Currently there is insufficient evidence, both in quality and quantity, to support the adoption of early diagnosis or screening programmes for dementia in primary care. When evidence develops to support diagnostic capabilities and therapeutic options for those diagnosed with early-onset dementia, the implementation of community-based screening programmes and early diagnosis should be re-evaluated. With additional sociological investigation to explore the psychosocial implications and meaning of dementia for individuals, family, friends, employers and for wider society will need to be considered further to better address current fears and stigmas related to diagnosis.

FIGURE AND TABLE LEGENDS

Figure 1: PRISMA Flow-Chart

Table 1: MEDLINE search strategy

Table 2: Characteristics of Included Studies

Table 3: Summary of critical appraisal results

CONFLICT OF INTEREST

None of the authors declare any conflict of interest in relation to this paper.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO Registration: CRD42015027719

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent was not required for this study design.

AUTHOR CONTRIBUTIONS

DESIGN RESEARCH: TOS; JC; FP; FC; AB; IM; BP; KL; CF

LITERATURE SEARCHING: TOS; FC; AB

DATA EXTRACTION/APPRAISAL: TOS; FC; AB

DATA ANALYSIS: TOS; FC; AB; JC; CF

INTERPRETATION OF THE DATA: TOS; JC; FP; FC; AB; IM; BP; KL; CF

PREPARED THE PAPER: TOS; JC; FP; FC; AB; IM; BP; KL; CF

AGREED FINAL MANUSCRIPT: TOS; JC; FP; FC; AB; IM; BP; KL; CF

GUARANTOR: CF

REFERENCES

1. Price. *Neurobiol.Aging*.2009;30:1026–36. [cited 2015 October 15]. Available at: www.alzheimers.org.uk/site/scripts/download_info.php?fileID =2226
2. The epidemiology, and impact of dementia. Current state and future trends, Background Paper Prepared for the World Health Organization Ministerial Conference on Global Action Against Dementia, March 2015, Professor Martin Prince, Dr Maeleenn Guerchet, Dr Matthew Prina. [cited 2015 October 15]. Available at: http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf?ua=1
3. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 88: 1337-42 (1998).
4. WHO, WHO & Alzheimer's Disease International. 2012. [cited 2015 December 18]. Available at: <https://www.alz.co.uk/research/WorldAlzheimerReport2012ExecutiveSummary.pdf>
5. Prince M, Byrce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement* 9: 63-75 (2013).
6. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 13:788-94 (2014).
7. Teipel S, Drzezga A, Grothe MJ, Barthel H, Chetelat G, Schuff N, et al. Multimodal imaging in Alzheimer's disease: validity and utility for early detection. *Lancet Neurol* 14: 1037-53 (2014).
8. Martin S, Fleming J, Cullum S, Denning T, Rait G, Fox C, et al. Exploring attitudes and preferences for dementia screening in Britain; contributions from carers and the general public. *BMC Geriatrics* 15: 110 (2015).
9. Higgins JPT, Green S. *Cochrane handbook of systematic reviews of interventions*. Wiley-Blackwell, Chichester, UK: 2008.
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 62: 1006-12 (2009).

11. CASP. Critical Appraisal Skills Programme. 2015. [cited 2015 October 8]. Available at: <http://www.casp-uk.net/#!/casp-tools-checklists/c18f8>
12. Perry M. Training family physicians and primary care nurses to provide diagnostic assessment of dementia: results of a randomized controlled trial. *Alzheimers Dementia* 7 Supp S498 (2011).
13. Iliffe S, Manthorpe J, Eden A. Sooner or later? Issues in the early diagnosis of dementia in general practice: a qualitative study. *Fam Pract* 20: 376-81 (2003).
14. Hansen EC, Hughes C, Routley G, Robinson AL. General practitioners' experiences and understandings of diagnosing dementia: factors impacting on early diagnosis. *Soc Sci Med* 67: 1776-83 (2008).
15. Manthorpe J, Iliffe S, Eden A. Early recognition of dementia by nurses. *J Adv Nurs* 44: 183-91 (2003).
16. Russell P, Banerjee S, Watt J, Adleman R, Agoe B, Burnie N, et al. Improving the identification of people with dementia in primary care: evaluation of the impact of primary care dementia coding guidance on identified prevalence. *BMJ Open* 3: e004023 (2013).
17. Banerjee S, Willis R, Matthews D, Contell F, Chan J, Murray J. Improving the quality of care for mild to moderate dementia: an evaluation of the Croydon Memory Service Model. *Int J Geriatr Psychiatry* 22: 782-788 (2007).
18. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189-198 (1975).
19. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* 1: 233-8 (1972).

20. Boise L, Camicioli R, Morgan DL, Rose JH, Congleton L. Diagnosing dementia: perspectives of primary care physicians. *Gerontologist* 39: 457-64 (1999).
21. Holsinger T, Boustani M, Abbot D, Williams JW. Acceptability of dementia screening in primary care patients. *Int J Geriatr Psychiatry* 26: 373-9 (2011).
22. Fowler NR, Boustani MA, Frame A, Perkins AJ, Monahan P, Gao S, et al. Effect of patient perceptions on dementia screening in primary care. *J Am Geriatr Soc* 60: 1037-43 (2012).
23. Fowler NR, Perkins AJ, Turchan HA, Frame A, Monahan P, Gao S, et al. Older primary care patients' attitudes and willingness to screen for dementia. *J Aging Res* 2015:423265 (2015).
24. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 9: 1-93 (2005).
25. Iracleous P, Nie JX, Tracy CS, Moineddin R, Ismail Z, Shulman KI, et al. Primary care physicians' attitudes towards cognitive screening: findings from a national postal survey. *Int J Geriatr Psychiatry* 25: 23-9 (2010).
26. Manthorpe J, Iliffe S. Timely recognition of dementia: community nurses' crucial roles. *Br J Community Nurs* 12: 74-6 (2007).
27. Fox M, Fox C, Cruickshank W, Penhale B, Poland F, Steel N. Understanding the dementia diagnosis gap in Norfolk and Suffolk: a survey of general practitioners. *Qual Prim Care* 22: 101-7 (2014).
28. Cahill S, Clark M, O'Connell H, Lawlor B, Coen RF, Walsh C. The attitudes and practices of general practitioners regarding dementia diagnosis in Ireland. *Int J Geriatr Psychiatry* 23: 663-9 (2008).

29. Pond CD, Mant A, Kehoe L, Hewitt H, Brodaty H. General practitioner diagnosis of depression and dementia in the elderly: can academic detailing make a difference? *Fam Pract* 11: 141-7 (1994).
30. Turner S, Iliffe S, Downs M, Wilcock J, Bryans M, Levin E, et al. General practitioners' knowledge, confidence and attitudes in the diagnosis and management of dementia. *Age Ageing* 33: 461-7 (2005).
31. Martin S, Kelly S, Khan A, Cullum S, Denning T, Rait G, et al. Attitudes and preferences towards screening for dementia: a systematic review of the literature. *BMC Geriatr* 15:66 (2015).
32. Boise L, Eckstrom E, Fagnan L, King A, Goubaud M, Buckley DI, et al. The rural older adult memory (ROAM) study: a practice-based intervention to improve dementia screening and diagnosis. *J Am Board Fam Med* 23: 486-98 (2010).
33. Iliffe S, Mitchley S, Gould M, Haines A. Evaluation of the use of brief screening instruments for dementia, depression and problem drinking among elderly people in general practice. *Br J Gen Pract* 44: 503-7 (1994).
34. Lawrence JM, Davidoff DA, Katt-Lloyd D, Connell A, Berlow YA, Savoie JA. Is large-scale community memory screening feasible? Experience from a regional memory-screening day. *J Am Geriatr Soc* 51: 1072-8 (2003).
35. Borson S, Frank L, Bayley PJ, Boustani M, Dean M, Lin PJ, et al. Improving dementia care: the role of screening and detection of cognitive impairment. *Alzheimers Dement* 9: 151-9 (2013).
36. Fox C, Lafortune L, Boustani M, Brayne C. The pros and cons of early diagnosis in dementia. *Br J Gen Pract* 63(612): e510-2 (2013).
37. Fox C, Lafortune L, Boustani M, Denning T, Rait G, Brayne C. Screening for dementia--is it a no brainer? *Int J Clin Pract*. 67: 1076-80 (2013).

38. Jacinto AF, Nitrini R, Brucki SM, Porto CS, de Mello Franco FG, de Albuquerque Citero V. The pros and cons of early diagnosis of dementia. *Br J Gen Pract* 63: 463 (2013).
39. Chinthapalli K. Reward doctors for early diagnosis of dementia, says think tank. *BMJ* 345: e8533 (2012).
40. Banerjee S, Wittenberg R. Clinical and cost effectiveness of services for early diagnosis and intervention in dementia. *Int J Geriatr Psychiatry* 24: 748-54 (2009).
41. Ashford JW, Borson S, O'Hara R, Dash P, Frank L, Robert P, et al. Should older adults be screened for dementia? It is important to screen for evidence of dementia! *Alzheimers Dement* 3: 75-80 (2007).
42. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J Neuropathol Exp Neurol* 71: 266–73 (2012).
43. Bond J, Graham N, Padovani A, Mackell J, Knox S, Atkinson J. Screening for cognitive impairment, Alzheimer's disease and other dementias: opinions of European caregivers, payors, physicians and the general public. *J Nutr Health Aging* 14: 558-62 (2010).
44. US Preventive Services Task Force, 2014. Screening for Cognitive Impairment in Older Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 160:I-20 (2014).
45. Public Health England. 2015. UK National Screening Committee on Dementia Screening Report. [cited 2015 November 27]. Available at: <https://www.gov.uk/government/news/recommendation-against-national-dementia-screening>
46. Boustani MA, Justiss MD, Frame A, Austrom MG, Perkins AJ, Cai X, et al. Caregiver and noncaregiver attitudes toward dementia screening. *J Am Geriatr Soc* 59: 681-6 (2011).

47. Justiss MD, Boustani M, Fox C, Katona C, Perkins AJ, Healey PJ, et al. Patients' attitudes of dementia screening across the Atlantic. *Int J Geriatr Psychiatry* 24: 632-7 (2009).
48. Petrella RJ, Lattanzio CN, Overend TJ. Physical activity counseling and prescription among Canadian primary care physicians. *Arch Intern Med* 167: 1774-81 (2007).
49. Kim S, Sargent-Cox KA, Anstey KJ. A qualitative study of older and middle-aged adults' perception and attitudes towards dementia and dementia risk reduction. *J Adv Nurs* 71: 1694-703 (2015).
50. Ydstebø AE, Bergh S, Selbæk G, Benth JS, Lurås H, Vossius C. The impact of dementia on the use of general practitioners among the elderly in Norway. *Scand J Prim Health Care* 33: 199-205 (2015).
51. Cantegreil-Kallen I, Pin S. Fear of Alzheimer's disease in the French population: impact of age and proximity to the disease. *Int Psychogeriatr* 24: 108-16 (2012).
52. Zeng F, Xie WT, Wang YJ, Luo HB, Shi XQ, Zou HQ, et al. General public perceptions and attitudes toward Alzheimer's disease from five cities in China. *J Alzheimers Dis* 43: 511-8 (2015).
53. Borson S, Scanlan J, Hummel J, Gibbs K, Lessig M, Zuhr E. Implementing routine cognitive screening of older adults in primary care: process and impact on physician behaviour. *J Gen Intern Med* 22: 811-7 (2007).

Figure 1: PRISMA Flow-Chart

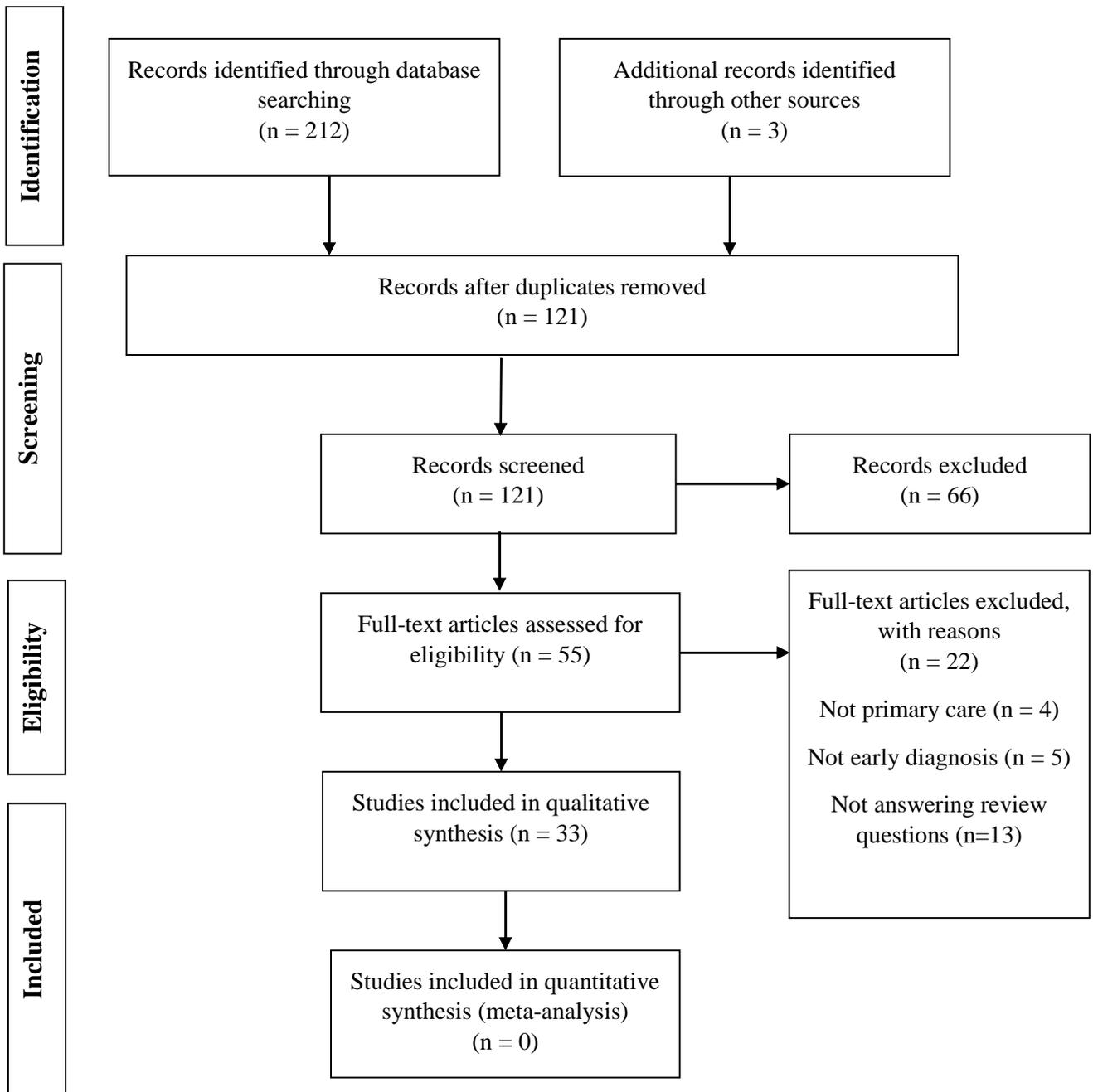


Table 1: MEDLINE search strategy

1. exp Dementia/
2. Dementia, Amnestic, Cognitive Disorders/
3. dement*.mp.
4. vascular dementia.mp.
5. alzheimer*.mp.
6. (lewy* adj2 bod*).mp.
7. (chronic adj2 cerebrovascular).mp.
8. (cerebr* adj2 deteriorat*).mp.
9. (cerebral* adj2 insufficient*).mp.
10. ("organic brain disease" or "organic brain syndrome").mp.
11. OR/1-10
12. exp Primary Health Care/
13. exp Community Health Services/
14. community physician.mp.
15. family doctor.mp.
16. general practi*.mp.
17. OR/12-16
18. diagnosis.mp.
19. screening.mp.
20. OR/18,19
21. AND/11,17,20

Table 2: Characteristics of Included Studies

Study Name	Origin	Study Design	Cohort Profession	Screening tool	Appraisal Quality
Ashford et al [41]	USA	Commentary	Not assessed	Not assessed	Not applicable
Banerjee et al [17]	UK	Mixed-methods analysis of implementation of a memory service	Multidisciplinary (physicians and nursing)	Not assessed	Low
Banerjee and Wittenberg [40]	UK	Health economic analysis of a memory service	Multidisciplinary (physicians and nursing)	Not assessed	Moderate
Boise et al [32]	USA	Quantitative analysis of implementation of Screening Programme	6 rural GP practices in Oregon USA including 18 clinicians and 26 medical assistants	Rural Older Adult Memory Evaluation	Moderate
Boise et al [20]	USA	Qualitative investigation with focus groups	78 primary care physicians	Not assessed	High
Bond et al [43]	France, Germany, Italy, Spain and the United Kingdom	Survey of carers, commissioners, GP and general public to dementia screening	1000 public responses, 250 caregivers, 50 commissions.	Not assessed	Moderate
Borson et al [35]	USA	Commentary	Not assessed	Not assessed	Not applicable
Borson et al [53]	USA	Quantitative analysis of implementation of Screening Programme	524 community-dwelling individuals assessed by 26 medical assistants	Mini-Cog	High
Boustani et al [46]	USA	Survey of attitudes towards dementia screening	81 people with dementia caregiving experience and 125 people without dementia caregiving experience	Not assessed	Moderate
Cahill et al [28]	Ireland	Survey of GPs and 2 focus groups	Survey: 300 GPs; Focus Group: 7 GPs in 1 urban and 1 rural practice	Not assessed	High
Chinthapalli [39]	UK	Commentary	Not assessed	Not assessed	Not applicable
Fowler et al [22]	USA	Quantitative analysis of attitudes towards screening programme	554 patients in primary care	Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC)	High

Fowler et al [23]	USA	Quantitative analysis of attitudes towards screening programme	400 patients in primary care	Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC)	High
Fox et al [36]	UK/USA	Commentary	Not assessed	Not assessed	Not applicable
Fox et al [37]	UK/USA	Commentary	Not assessed	Not assessed	Not applicable
Fox et al [27]	UK	Survey of GPs	113 GPs in East of England	Not assessed	Moderate
Hansen et al [14]	Australia	Qualitative investigation with focus groups.	24 GPs in urban and rural practices	Not assessed	High
Holsinger et al [21]	USA	Quantitative analysis of implementation of Screening Programme	345 patients in primary care	Dementia Screening and Perceived Hames (SAPH) questionnaire	High
Iliffe et al [13]	UK	NGT consensus during workshop	247 GPs; 146 CN; 36 PN; 79 CMHN	Not assessed	High
Iliffe et al [33]	UK	Quantitative analysis of implementation of Screening Programme	2 GP practices in London UK	MMSE and clinical history/examination	High
Iracleous et al [25]	Canada	Survey on GP perceptions of screening for dementia.	249 GP responses	Not assessed	Moderate
Jacinto et al [38]	Brazil	Letter	Not assessed.	Not assessed	Not applicable
Justiss et al [47]	USA	Survey of attitudes towards dementia screening	245 older adults in USA n=125) and UK (n=120)	Not assessed	Moderate
Lawrence et al [34]	USA	Quantitative analysis of implementation of Screening Programme	659 community-dwelling individuals	7-Minute Screen	High
Manthorpe et al [15]	UK	Survey data from workshop	24 one-day workshops across 21 UK cities with primary care staff	Not assessed	High
Manthorpe et al [26]	UK	Survey data from workshop	1536 CN; 36 PN; 79 CMHN	Not assessed	High
Martin et al [31]	UK	Qualitative analysis of workshop	36 people; 8 Alzheimer Society Research Network volunteers	Not assessed	High
Martin et al [8]	UK	Systematic review of patients/carer attitudes towards screening	29 eligible papers	Not assessed	Not applicable

Perry [12]	Netherlands	Randomised Controlled Trial	105 family physicians and primary care nurses	Not assessed	Moderate
Pond et al [29]	Australia	Educational support to implement diagnosis in a pre-test post-test study	13 GPs in Australian urban practices. 200 patients	The Canberra Interview for the Elderly (CIE) and MMSE.	Moderate
Russell et al [16]	UK	Quantitative analysis of a Read Code detection system	23 GP practices in 19 regions of London	Not assessed	Moderate
Turner et al [30]	UK	Survey of GPs	127 GPs from 20 Scottish and 16 London GP practices	Not assessed	Moderate
US Preventive Services Task [44]	USA	Recommendations/Guidelines	Not assessed	Not assessed	Not applicable

CMHN – community mental health nurses; CN – community nurses; GP – general practitioners; MMSE – mini-mental state examination; NGT – Nominal Group Technique; PN – practice nurses

Table 3: Summary of critical appraisal results

Criterion	Banerjee et al [17]	Banerjee and Wittenberg [40]	Boise et al [32]	Boise et al [20]	Bond et la [43]	Borson et al [53]	Boustani et al [46]	Cahill et al [28]	Fowler et al [22]	Fowler et al [23]	Fox et al [27]	Hansen et al [14]
Did the study address a clearly focused issue?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the cohort recruited in an acceptable way?	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
Was the exposure accurately measured to minimize bias?	X	X	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
Was the outcome accurately measure to minimize bias?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Have the authors identified all important confounding factors?	X	X	X	U	X	U	X	X	✓	✓	X	✓
Was the follow up of the subjects complete enough?	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the follow up of subjects long enough?	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Where confidence intervals presented?	X	X	X	N/A	X	X	X	N/A	✓	✓	X	N/A
Were the results generalisable to the general population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Do the results of this study fit with other available evidence?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ - satisfied; X – not satisfied; N/A – not applicable; U – unclear

Criterion	Holsinger et al [21]	Iiiffe et al [13]	Iiiffe et al [33]	Iracleous et al [25]	Justiss et al [47]	Lawrence et al [34]	Manthorpe et al [15]	Manthorpe et al [26]	Martin et al [31]	Perry [12]	Pond et al [29]	Russell et al [16]	Turner et al [30]
Did the study address a clearly focused issue?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the cohort recruited in an acceptable way?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the exposure accurately measured to minimize bias?	✓	N/A	✓	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	✓
Was the outcome accurately measure to minimize bias?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Have the authors identified all important confounding factors?	✓	U	X	X	X	U	U	U	✓	U	X	X	X
Was the follow up of the subjects complete enough?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓
Was the follow up of subjects long enough?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Where confidence intervals presented?	✓	N/A	✓	X	X	X	✓	✓	N/A	X	X	X	X
Were the results generalisable to the general population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Do the results of this study fit with other available evidence?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ - satisfied; X – not satisfied; N/A – not applicable; U – unclear