A systematic rapid evidence assessment of late diagnosis

Jenny Caird, Kate Hinds, Irene Kwan and James Thomas

EPPI-Centre
Social Science Research Unit
Institute of Education
University of London

REPORT

The authors of this report are:

Jenny Caird, Kate Hinds, Irene Kwan and James Thomas (EPPI-Centre).

Conflicts of interest

There were no conflicts of interest in the writing of this report.

Contributions

The opinions expressed in this publication are not necessarily those of the EPPI-Centre or the funders. Responsibility for the views expressed remains solely with the authors.

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Abbreviations

A&E	Accident & Emergency
AEDs	Antiepileptic Drugs
AIDS	Acquired Imunodeficiency Syndrome
AMI	Acute Myocardial Infarction
AMSTAR	Assessment of Multiple Systematic Reviews
AOR	adjusted Odds Ratio
ARD	Acute Renal Disease
AUC	Area Under Curve
BMI	Body Mass Index
BTS	British Thoracic Society
CAPTIM	Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction
CBT	Cognitive Behavioural Therapy
CD4	Cluster of Differentiation 4 Cell Count
CDC	Centers for Disease Control and Prevention
CDSS	Clinical Decision Support System
CI	Confidence Intervals
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRAU	Community Respiratory Assessment Unit
CT	Computed Tomography
DETECT	Dublin East Treatment and Early Care Team
DSM	Diagnostic and Statistical Manual
DTB	'door to balloon'
DUP	Duration of Untreated Psychosis
ECG	Electrocardiogram
ED	Emergency Department
EDIE	Early Detection and Intervention Evaluation
EEG	Electroencephalogram
E-EPA	Ethyl-eicosapentaenoic Acid
EIPS	Early Initial Prodromal State of Psychosis

EIS	Early intervention Services
EPIP	Early Psychosis Intervention Program
EPPIC	Early Psychosis Prevention and Intervention Centre
EPPI-Centre	Evidence for Policy and Practice Information Centre
ESP	Erythropoeisis-Stimulating Proteins
ESRD	End Stage Renal Disease
ETS	Enhanced Tuberculosis Surveillance
FAST	Facial weakness, Arm weakness, Speech problems, Time to call 999
FEP	First Episode Psychosis
FEV1	Forced Expiratory Volume in 1 Second
FL	Fibrinolysis
FVC	Forced Vital Capacity
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GFR	Glomerular Filtration Rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HAART	Highly active anti-retroviral treatment regimens
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSE	Health Survey of England
I^2	A measure used to quantify heterogeneity
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQ	Intelligence quotient
IQR	Inter-Quartile Range
LEO-CAT	Lambeth Early Onset Crisis Assessment Team Study
LLN	Lower Limit of Normal
LMIC	Low and Middle Income Countries
MD	Mean Difference
MINAP	Myocardial Ischeamia National Audit Project
MRC	Medical Research Council

MRI	Magnetic Resonance Imaging
MSM	Men-who-have-sex-with-men
NAO	National Audit Office
NCD	National Clinical Director
NHS	National Health Service
NIAP	National Infarct Angioplasty Project
NICE	National Institute for Clinical Excellence
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NPSA	National Patient Safety Agency
NS	Not significant
nSTEMI	non-ST-segment Elevation Myocardial Infarction
NZ	New Zealand
OIs	Opportunistic Infections
OPUS	intensive early-intervention program (Swedish)
OR	Odds Ratio
p	Probability Value
PANSS	Positive and Negative Syndrome Scale
PCP	Primary Care Provider
PCT	Primary Care Trust
PEPP	Prevent and Early Intervention Program for Psychosis
PPCI	Primary Percutaneous Coronary Intervention
PPV	Positive Predictive Value
QALYS	Quality Adjusted Life Years
QATSO	Quality Assessment Tool for Systematic Reviews of Observational Studies
QOF	Quality Outcomes Framework
QOL	Quality of Life
RAISE	Recovery After an Initial Schizophrenia Episode
REACT	Rapid Early Action for Coronary Treatment
REDIRECT	Birmingham Early Detection in Untreated Psychosis Trial
RFH	Royal Free Hospital
ROC	Receiver operating characteristic
RR	Risk Ratio

RRT	Renal Replacement Therapy
rt-PA	Recombinant Tissue Plasminogen Activator
SAPS	Scales for the Assessment of Positive Symptoms
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
SOFAS	Social and Occupational Functioning Assessment Scale
SREA	Systematic Rapid Evidence Assessment
STEMI	ST elevation myocardial infarction
STI	Sexually Transmitted Infection
SuperEDEN	Sustaining Positive Engagement and Recovery project
SWEDES	Swedish Early Decision Project
TB	Tuberculosis
TB-PBPR	TB Process-Based Performance Review
TIA	Transient Ischaemic Attack
TIPS	The Treatment and Intervention in Psychosis project
UK	United Kingdom
US	United States of America
WHO	World Health Organisation
WMD	Weighted mean difference

Executive Summary

Background

Delayed diagnosis results in serious consequences for patients and healthcare professionals and has the potential to incur substantial financial costs.

There are numerous points at which a delay in diagnosis can occur: in the help-seeking behaviour of the patient; access to healthcare (waiting for an appointment); clinical assessment in primary and secondary care (not investigating or misdiagnosing); test ordering (waiting for tests); test results (test results lost or misdirected); and referral (referral waiting time, referral missed, prioritisation incorrect). Hansen et al. (2008) delineate three categories of delay in diagnosis: 'patient delay' (attributable to the patient); 'doctor delay' (attributable to clinical staff); and 'system delay' (attributable to administrative and procedural errors). There may also be time lost between diagnosis and referral to, or initiation of, treatment ('treatment delay').

Kostopoulou et al. (2008) describe common features of diagnostic difficulty including: atypical presentation; non-specific presentation; rarity of condition; the presence of co-morbidity; and perceptual features susceptible to subjective judgement. Demographic characteristics influencing delayed diagnosis include (among others) age, gender, socioeconomic status and level of education (McDonald et al. 2006, Mitchell et al. 2008, Scott et al. 2006).

While a substantial body of research focussing upon cancer suggests that late diagnosis leads to increased morbidity and mortality, the state of the evidence base for other conditions is less clear. This systematic rapid evidence assessment (SREA) has been commissioned to identify and characterise this research across a range of conditions.

Review question

What is the nature and extent of UK evidence on delayed diagnosis?

Methods

A systematic rapid evidence assessment (SREA) represents the only way in which a broad policy question may be answered within a tight timescale. A SREA was conducted in two phases. First, a systematic map was produced to answer the question *"What is the nature and extent of UK evidence on delayed diagnosis?"* The map contained a brief overall characterisation of the distribution of studies and a quality assessment of relevant systematic reviews. The map was used to focus discussion with policy customers in order to inform decisions about policy relevant topics for the second phase: an in-depth review and synthesis of the findings of systematic reviews concerning late diagnosis in chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, type I diabetes, epilepsy, HIV, myocardial infarction, psychosis, stroke and tuberculosis, and a review of the results of UK primary studies examining late diagnosis in chronic obstructive pulmonary disease (COPD), tuberculosis and epilepsy. The two types of studies

included in the second phase reflected the available evidence: while there were relevant systematic reviews on which we could draw for most areas, this was not the case for COPD, tuberculosis and epilepsy; we therefore reviewed primary studies in order to fill this particular gap.

Key Findings

Study selection
We identified 43 systematic reviews investigating late diagnosis. UK primary studies investigating late diagnosis numbered 606, of which 11 investigated late diagnosis and COPD, 12 late diagnosis and tuberculosis and 4 late diagnosis and epilepsy.

Map of research activity
At the initial coding, using abstracts only, we found 35 systematic reviews examined late diagnosis and specific conditions, and another nine focused upon the phenomenon of late diagnosis across conditions or in a particular health care setting. The majority of the reviews were published in the last four years.

Nineteen reviews focused upon the prevalence of delayed diagnosis. The majority of the reviews (n=22) included observational studies with non-experimental research methods. Trials or -interventions to reduce delay were examined in a minority of studies (systematic reviews n=15). Determinants of delay were investigated in 25 studies.

Delay was concentrated in primary healthcare (n=29), with studies examining doctor delay (n=22) and patient delay (n=21). Very few studies mentioned delay in secondary healthcare (n=5).

We only found three reviews examining the cost implications of delayed diagnosis.

Of the 11 studies examining late diagnosis of COPD, six looked at prevalence, three at determinants, one at outcomes and four at interventions. For TB, five studies looked at prevalence, two at outcomes, four at determinants, and two at interventions. For epilepsy, one investigated prevalence, one interventions and three outcomes.

Results
An overview of the findings of the systematic rapid evidence assessment are presented in Table I overleaf.

Table I: Overview of the findings of the systematic rapid evidence assessment

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Number of systematic reviews	5	0	3	3	1	0	2	6	7	4	4 (limited UK relevance)
UK primary studies	-	12	-	-	-	4	-	-	-	-	12
Metrics for late diagnosis	Stage	Stage	Severity		Keto-acidosis		CD4 count	Death	DUP	Death	
Is late diagnosis or under-diagnosis common?	~20% late referral	~80%	✓	ND	16-51%	ND	✓	ND	ND	✓	✓
Patient factors associated with late diagnosis	(Late referral)										
Age	?	Older	?	Older	<5yrs	ND	ND	? Older	ND	TIA Ø	Older
Gender	Ø	Ø	♀	ND	♀	ND	ND	♀	Ø	TIA Ø	♀
Ethnicity	Ø	ND	ND	ND	Minorities	ND	ND	Ø	Ø	ND	White
SES	?	ND	ND	ND	Lower	ND	ND	Lower	Ø	ND	Lower
Education	ND	ND	Lower	ND	Lower	ND	ND	Ø	ND	ND	Lower
Marital Status	ND	ND	Single	ND	n/a	ND	ND	Single	ND	ND	ND
Family History	Protective	ND	ND	ND	Protective	ND	ND	ND	ND	ND	ND
Location	?	Urban	Rural	ND	Ø	ND	ND	Ø	ND	ND	Rural

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Clinical Factors											
Atypical symptoms	ND	ND	ND	ND	?	ND	ND	ND	ND	ND	Extra-pulmonary
Co-morbidities	?	Asthma	Depression	ND	Infection; fever	ND	ND	Diabetes Ø Hypertension Ø	ND	ND	ND
Misattribution	ND	Asthma	Depression	ND	✓	ND	ND	ND	ND	ND	✓
Non-specific symptoms	ND	✓	Milder cases	ND	ND	ND	ND	ND	ND	ND	✓
Severity	ND	Milder cases	Milder cases; patient impair-ment	Milder cases	?	ND	ND	Milder cases	ND	ND	ND
General Practice Factors											
Knowledge / Training	Stage recog-nition; Referral criteria	Spirom-etry	✓	ND	ND	ND	ND	ND	ND	ND	✓
Clinical attitudes	ND	ND	Nihilism; fear; discomfort	ND	ND	ND	GP anxiety/ reticence	ND	ND	ND	ND
Consultation time	ND	ND	✓	ND	ND	ND	ND	ND	ND	ND	✓
Frequency of contact	ND	ND	✓	ND	ND	ND	ND	ND	ND	ND	Continuity
Communication	✓	ND	✓	ND	ND	ND	✓	ND	ND	ND	✓

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Outcomes											
Mortality	↑	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hospital admissions / length of stay	↑ Initial stay	↑ admissions	ND	ND	ND	ND	ND	ND	ND	ND	↑ In-patient care
Morbidity	↑	↑	ND	ND	ND	↑	↑	ND	↑	ND	ND
Remission	n/a	n/a	n/a	ND	ND	↓	ND	ND	↓	ND	ND
Costs	↓ earlier referral	ND	ND	ND	ND	↑ over-diagnosis	ND	ND	ND	ND	↓ outreach service
Interventions	Early referral	Case finding	Doctor education	ND	ND	Case review	ND	Mass media campaigns; pre-hospital ECG; primary angioplasty; thrombolysis	EIS; mass media campaign	mass media camp-aign; doctor educat-ion	Reminder systems; Doctor education
CKD Chronic Kidney Disease; COPD Chronic Obstructive Pulmonary Disease; HIV Human Immunodeficiency Virus; MI Myocardial Infarction; TB Tuberculosis; TIA Transient Ischaemic Attack; SES Socio-economic status; DUP Duration of Untreated Psychosis; EIS Early Intervention Services ? = Results mixed/conflicting/unclear; Ø = no association; ND = No data; n/a = not applicable; ↓ = decrease; ↑= increase; ♀= female; ♂ = male											

We present the key findings from each chapter covering the conditions reviewed. We then present the information sent to us by the National Clinical Directors (NCDs) that updates the information in the reviews and puts a UK perspective on these issues. The exceptions are dementia, where the director felt the chapter was an adequate description of the current situation in this country; and tuberculosis, where the feedback led us to synthesize current UK research, as the systematic reviews contained too much information from healthcare systems that are very different to the UK context.

Chronic Kidney Disease

We found five systematic reviews relating to delayed referral (as variously defined in individual studies) for chronic kidney disease (Black et al. 2010; Chan et al. 2007, Kahn and Amedia 2008, Navaneethan et al. 2008, Smart and Titus 2011).

The proportion of referrals occurring within four months of the need to start dialysis ranged between 20% and 50%. Two primary studies found evidence to suggest that approximately 40% of late referrals were attributable to patient non-compliance with appointments.

There was no evidence that gender and ethnicity were associated with late referral for chronic kidney disease. It was unclear whether age, socio-economic status, co-morbidities or geographical barriers to access influenced the timing of referral.

Doctors' lack of knowledge and awareness of guidelines, inadequate training and faulty communication between primary care doctors and nephrologists were identified as barriers to early referral.

Late referral resulted in unfavourable outcomes: significantly increased mortality; a prolongation of initial hospital stay; lower uptake of peritoneal dialysis; permanent access was less likely and temporary access more likely; erythropoietin usage was lower; and serum creatinine levels were higher and haemoglobin levels were lower as compared with patients referred early to nephrology care.

There is evidence to suggest that earlier referral is associated with lower costs.

Discussion of Recent Primary Research

Recent research from the UK indicates that late referral to nephrology is a problem that the health service is beginning to tackle. Eleven centres (Basildon, Bradford, Dorset, Leeds, Middlesbrough, Nottingham, Oxford, Portsmouth, Sheffield, Stevenage and Wolverhampton), supplying data for approximately 11,000 patients between 2004 and 2009 show that the proportion of patients presenting less than three months before initiation of RRT had fallen from 27.1% in 2004 to 17.0% in 2009, possibly as a result of the publication of national clinical guidelines or the quality and outcomes framework initiative (UK Renal Registry 2010). Udayaraj et al. (2011) attributed a falling trend and lower incidence of late referrals at an Oxford hospital unit between 2003 and 2008 to implementation of automated estimated glomerular filtration rate reporting and increased awareness of CKD in primary care.

In a similar vein, Farmer et al. (*in press*) assessed the impact of a computerised clinical decision support system (CDSS) to screen patients regularly having serum creatinine tests in primary care and found that six percent of the intervention group (n=98) were referred less than 90 days prior to commencing RRT as opposed to 25% of those not exposed to CDSS (n=353). Furthermore, those patients referred late were subdivided into those where the requirement for RRT was predictable (sustained GFR<30 mL/min/1.73m^2 or rapidly declining renal function) and those not predictable. In this group 2% (n=2) of those exposed to CDSS were referred less than 90 days prior to commencing RRT as opposed to 15% (n=52) of those not exposed to CDSS (Farmer et al. *in press*).

With respect to the demographic determinants of delayed referral ,the findings of the UK Renal Registry Report (2010) were in accordance with our own, although they reported that patients who presented late were significantly older than patients who presented more than 90 days before dialysis initiation [median age 67.0 *vs* 64.7 years, p < 0.0001].

Chronic Obstructive Pulmonary Disease (COPD)
No systematic reviews addressing late diagnosis and COPD were identified, but 12 primary studies examining this issue in the UK were found. After critical appraisal, 11 of these studies were included within our review.

There is considerable under-diagnosis of COPD with most people with COPD being undiagnosed. Some regional variation has been identified; late diagnosis seems to be particularly marked in urban centres, particularly London.

Diagnostic rates seem to be affected by GP and nurse supply. Spirometry and reversibility testing were not uniform across all practices and areas, and staff reported a lack of confidence and training in the use of spirometers and interpretation of results.

Under diagnosis was associated with hospital admissions for exacerbations.

There was no information about the cost implications of delay in the included primary studies.

Strategies to improve diagnosis included case finding and using specialist services for respiratory assessment.

Discussion of Recent Research
Avoiding crises is important for the patient as frequent exacerbations result in significantly faster decline (Donaldson et al. 2002) and a greater risk of mortality (Soler-Cataluna et al. 2005). Nevertheless, it has been reported elsewhere that exacerbations (with attendant hospitalisation and risk of death) are common even for those with moderate stages of the disease (Hurst et al. 2010).

Exacerbations, leading to hospitalisation, may also be avoided if patients with the condition are recognised and treated earlier (Celli et al. 2008, Seemungal et al. 1998). Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009).

Dementia

We found three systematic reviews examining late diagnosis and dementia (Bradford et al. 2009, Koch et al. 2010, Koch and Iliffe 2011).

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases.

Fear of a diagnosis affected patients and families, and made them reluctant to seek help. Fears centred round stigma, loss of independence and beliefs that nothing could be done. Primary care physicians shared the therapeutic nihilism of their patients and worried that a diagnosis would bring expectations of care that they could not fulfil.

Doctors acknowledged their difficulties in recognising the early stages of dementia and conducting tests in the short time available in a typical surgery consultation.

There was no information regarding either the outcomes or cost implications of late diagnosis of dementia in the included reviews.

Educational interventions increased healthcare practitioners' knowledge of dementia. Specifically, decision support software, practice based workshops and in- home assessment by nurses increased detection rates.

Depression

We found three reviews that examined late diagnosis in relation to depression (Cepiou et al. 2007, Das et al. 2006, Mitchell et al. 2011).

GPs and other non-psychiatric physicians were more likely to recognise people who did not have depression, than identify those who had the condition.

The evidence suggested that older people may be less likely to be diagnosed.

The milder stages of the disease were more difficult to recognise.

Discussion of Recent Research

Our findings echo the NICE guidelines which have cited studies suggesting that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient–doctor relationship and it is the milder forms, which are more likely to recover spontaneously, that go undetected and untreated (National Institute for Health and Clinical Excellence, 2010).

Attempts to improve recognition and diagnosis of depression in primary care are reflected in the Quality and Outcomes Framework (QOF) indictors of the GP contract. Quality Indicator DEP 1 encourages the screening of patients by making a record of the percentage of patients with diabetes and/or heart disease for whom case finding for depression has been undertaken on one occasion during the previous 15 months (NHS Evidence Clinical Knowledge Surveys, 2009). Recently, there has also been more focus on recognition by clinicians in acute hospital settings with an emphasis on co-morbidities, which (with respect to long-term conditions) most commonly include depression and dementia (personal

communication via email 20.06.12, from Dr Hugh Griffiths, National Clinical Director for Mental Health).

The Improving Access to Psychological Therapies (IAPT) programme which supports the implementation of National Institute for Health and Clinical Excellence (NICE) guidelines for people suffering from depression and anxiety disorders anticipates that by 2015 a nationwide roll-out of psychological therapy services for adults will be completed, a stand-alone programme for children and young people will be initiated, and models of care for people with long-term physical conditions, medically unexplained symptoms and severe mental illness will be developed, with estimated savings of up to £272 million for the NHS and £700 million for the public sector (IAPT 2012).

Type I Diabetes
We found one systematic review relating to delayed diagnosis in type I diabetes (Usher-Smith et al. 2011). Usher-Smith and colleagues examined factors associated with the presence of diabetic ketoacidosis at diagnosis of new onset, previously undiagnosed type I diabetes in children and young adults.

Four studies within Usher-Smith et al. (2011) reported a substantial proportion (16–51%) of children experiencing delayed diagnosis (>24 hours for any reason).

Children aged five years or less, from an ethnic minority or having parents with lower educational or socio-economic status were more likely to present with diabetic ketoacidosis. One study showed that girls were more likely to experience a delayed diagnosis but did not have an increased risk of severe diabetic ketoacidosis.

A delay of more than 24 hours between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with a four-fold increased risk of presenting with diabetic ketoacidosis.

One multicentre study included within Usher-Smith et al. (2011) showed that across Europe a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of diabetic ketoacidosis in children.

Discussion of Recent Research
Further information regarding the determinants of delayed diagnosis and opportunities for improving the time to diagnosis of type I diabetes may be provided by as yet unpublished data from the Early Care Survey, conducted in the UK. The newly-established regional paediatric diabetes network system and the Association of Children's Diabetes Clinicians has been used to gather approximately 250 responses over a three month period in this national audit of the pre-hospital experience of parents of children newly diagnosed with diabetes. The influence of factors including family structure, parents' educational level and socio-economic status upon delays to diagnosis (and the development of diabetic ketoacidosis) are being examined. Results from the audit will be available in late 2012 (Personal

communication via email on 2nd May 2012 from Dr Julie Edge, Consultant in Paediatric Diabetes, Oxford Children's Hospital).

Epilepsy
Two systematic reviews were found relating to the misdiagnosis of epilepsy rather than delayed diagnosis of epilepsy (Chapman et al. 2011, Juarez-Garcia et al. 2006). Therefore, we synthesized four primary studies from the UK.

The four primary studies provided very limited information about late diagnosis. However, experts recognize that it is a problem, related, partly, to late presentation. It is possible that over-diagnosis may present a more significant problem for this condition in adults.

In a UK national study, 27% of infants suffering from infantile spasms had a lead time to treatment of over two months.

Late treatment may contribute to developmental delay in children, and, in older patients, to an increased likelihood that the sufferer would not become seizure free after treatment.

One hospital managed to reduce the number of undetermined cases of epilepsy via case review and checks by independent neurologists.

Discussion of Recent Research
First seizure clinics have been established in several centres to ensure that patients receive the right advice and treatment. It is not considered clinically acceptable for patients to be put on routine waiting list for local neurologists after their first seizure as the opportunity for early intervention will be lost (personal communication from Dr Chris Clough, consultant neurologist, Kings College Hospital).

Recent NICE guidelines, published in 2012, on the diagnosis of epilepsy and training by the British Paediatric Neurology Association, may improve the situation for affected children and their families. An audit by the Royal College of Paediatrics and Child Health, due to report in September 2012, may throw further light on the problem of diagnosing epilepsy in children (personal communication from Dr Edward Wozniak, paediatrics advisor, Department of Health).

HIV
We found two systematic reviews relating to the delayed diagnosis of HIV (Chen et al. 2011, Deblonde et al. 2010).

Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis.

Fear of disclosure was identified as a barrier to testing among African communities in the UK.

Uptake of testing was inhibited among migrants who thought that HIV status might have a bearing on the immigration process.

GPs were reluctant to discuss HIV testing with patients, even those from high-risk groups, and preferred to refer patients elsewhere for testing.

There was no information about the prevalence, outcome or cost implications of delayed diagnosis of HIV infection, and none of the primary studies within the included reviews examined interventions to reduce delayed diagnosis of HIV infection.

Discussion of Recent Research

Data from the Health Protection Agency suggests that the late diagnosis of HIV is substantial: of the 6,658 new HIV diagnoses made in 2010, 50% were late (with a CD4 cell count of <350/mm^3) and 28% very late (with a CD4 count <200 cells/mm^3) (Health Protection Agency, 2011).

A late (CD4 count <350/mm^3) or very late (CD4<200/mm^3) HIV diagnosis is associated with increased morbidity and mortality: a quarter of deaths among HIV positive individuals in the UK are among those diagnosed too late for effective treatment, and individuals starting antiretroviral therapy with a CD4 count below 350 cells/mm^3 have a significantly increased risk of contracting opportunistic diseases (Health Protection Agency, 2011). Furthermore, undiagnosed individuals have been estimated to have a rate of onward transmission three times higher than those who are diagnosed with HIV infection, and be more than twice as likely to have unprotected sex (Marks et al. 2006).

Recent UK primary research has demonstrated that the annual treatment cost for HIV infected individuals decreased as CD4 count increased, with the biggest differences observed between starting highly active anti-retroviral treatment regimens (HAART) with a CD4 count ≤200 cells/mm^3 compared with a CD4 count >200 cells/mm^3 (Beck et al 2011a). Beck and colleagues concluded that while starting patients on a first-line HAART regimen at CD4 counts ≤350 cell/mm^3 would increase the number of patients receiving HAART and initially increase the population costs of providing HIV services, earlier treatment on cost-effective regimens would maintain patients in better health and result in reduced use of health and social services (thereby generating fewer treatment and care costs and enabling people living with HIV to remain socially and economically active members of society). Nevertheless, Beck et al. (2011b) note that 25% of HIV positive individuals accessing services continue to present with a CD4 count ≤200 cells/mm3, which highlights the need to investigate the cost-effectiveness of testing and early treatment programs for key populations in the UK.

The National Institute for Health and Clinical Excellence has produced a costing model which estimates that a shift of 1% of patients being diagnosed at an earlier stage of disease effects a reduction in treatment costs and creates savings: approximately £212,000 a year for men who have sex with men and £265,000 a year for black Africans in England. The cumulative effect of onward transmissions avoided means that over time savings would increase and become greater (NICE, 2011).

Eight Department of Health funded projects conducted in high prevalence areas in the UK between 2009 and 2010 resulted in more than 10000 HIV tests being performed and appeared to be effective in detecting new cases: together they generated a total of 50 newly diagnosed individuals giving an overall positivity of five per 1000 tests. The estimated annual cost of expanding testing into general medical services nationally in areas of high prevalence with coverage of 75% would be £1.3 million: the cost for an average high prevalence PCT would be £19,000 per 100,000 people (Health Protection Agency, 2010).

Finally, since the introduction of the universal offer of an HIV test as part of routine antenatal care in 1999, uptake of HIV testing among women in antenatal care has reached 95% nationally. The proportion of women who remain undiagnosed after delivery fell from 27% in 2000 to 12% in 2009 and the estimated proportion of newborns at risk of HIV infection who become infected fell from 8% to 2% between 2000 and 2008 (Health Protection Agency, 2010).

Myocardial Infarction

We found six systematic reviews that examined ST-segment elevated myocardial infarction (STEMI) (Brainard et al. 2005, Hewitt et al. 2004, Dubayova et al. 2010, Morrison et al. 2006, Boersma et al. 2006, De Luca et al. 2008).

Much of the information in the reviews is out of date as medical practice in this field has moved on since they were published.

Patient delay is the most difficult area to tackle and evidence from public awareness campaigns is weak, suggesting that the increase in the use of emergency services is not offset by gains in earlier diagnosis.

Pre-hospital ECG, administered by paramedics, decreases the time to treatment.

Primary percutaneous coronary intervention is the treatment of choice despite the need to transfer some patients to a specialist centre.

There is no information on prevalence, outcomes or costs in the reviews.

Discussion of Recent Research

Recent UK research by Quinn et al. (forthcoming) on a large dataset of patients from the MINAP (Myocardial Ischaemia National Audit Project) registry found that pre hospital ECG enabled patients to receive treatment within the recommended time ('call to balloon' time $\leq$ 90 mins (27.88% vs 21.42%, OR 0.73, 95% CI 0.65-0.81) for PPCI, and 'door to needle' time $\leq$ 30 mins (90.61% vs 83.68%, OR 0.54, 95% CI 0.47-0.62) for those receiving fibrinolytic therapy in hospital). This, in turn, affected mortality, with lower hospital (4.0% vs 4.7%, OR 0.91, 95% CI 0.86-0.95) and 30 day (7.4% vs 8.2%, OR 0.95, 95% CI 0.91-0.99) mortality for STEMI patients who received reperfusion treatment. Pre hospital ECG use increased from 48% to 68% over the period of the study (January 2005 to December 2009), but overall only 50.3% of emergency patients received pre-hospital ECG.

In 2002 few UK centres offered PPCI, but evidence, from trials and observational studies (Huynh et al. 2009), showed that the procedure offered greater benefits in

terms of survival and complications than thrombolysis treatment. The National Infarct Angioplasty Project (NIAP) was established to collect and analyse data from seven PPCI pilots from April 2005 to March 2006. In 2008, they concluded their study and reported that PPCI could be delivered within acceptable treatment times. Of those patients admitted directly to a catheter laboratory in a PPCI centre, 98% achieved a 'door to balloon' (DTB) time of less than 90 minutes (NIAP 2008).

Since 1999, MINAP has collected clinical audit data from a network of hospitals on the care of patients with heart attack. In 2011, it reported an increase of centres offering PPCI over the last 10 years from 86 in England and 2 in Wales to 133 and 8 respectively. Ninety percent of patients in England were treated with PPCI within 90 minutes of arriving in hospital, the recommended time interval. For PPCI, a greater percentage of patients were treated within the recommended time, i.e. 150 minutes from calling for professional help, if they were taken directly to a heart attack centre – 88% in England, 76% in Wales, 89% in Belfast (MINAP 2011).

Since the publication of the National Service Framework for Coronary Heart Disease in 2000 (Dept of Health 2000), NICE has produced guidelines for the management of nSTEMI (National Clinical Guidelines Centre 2009) and guidelines for STEMI will be published soon, based on more recent primary studies. Data from a recent study looking at delays to reperfusion across four regions of the world show that Europe (including data from the UK) has the shortest times to PPCI and fibrinolysis (Spencer et al. 2010).

Psychosis
We found seven systematic reviews relating to delayed diagnosis for psychosis (Anderson et al. 2010, Bird et al. 2010, Farooq et al. 2009, Lloyd-Evans et al. 2010, Marshall et al. 2006, Marshall and Rathbone 2011, Perkins et al. 2005).

The duration of untreated psychosis, i.e. the time interval between symptom initiation and diagnosis and/or treatment, was found to have a median of 21.6 weeks, with a range of four to 68 weeks.

Longer duration of untreated psychosis (DUP) is associated with greater severity of positive symptoms after treatment, greater severity of global symptoms after treatment, poorer social functioning, more likely relapse and lower rates of remission.

We found no information about cost implications in the included reviews.

The results of studies reporting on the impact of multi-focus awareness campaigns on reducing DUP were mixed and conflicting.

Specialised teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, larger trials are needed to confirm this.

Results from small scale trials, which have not been replicated, suggest that E-EPA oil, the anti-psychotic amisulpride, and a combination of anti-psychotics and CBT are strategies that warrant further investigation for the prevention of transition to psychosis.

Discussion of Recent Research

The reviews do not tell us where in the diagnostic process delay is most likely to occur, but primary research conducted by Brunet et al. (2007) in the UK indicated that the median delay within secondary services was over seven times the delay in the referral pathway, with a mean delay in mental health services accounting for 35% of overall DUP. Data from Anderson et al. (2010) suggests that those from ethnic minorities are more likely to experience a pathway into care that involves emergency services or an element of compulsion. Nevertheless, a UK study (Morgan et al. 2006) found no evidence that African-Caribbean or Black African patients experienced longer periods of untreated psychosis than White British patients prior to first contact with services.

There is good evidence that early intervention services (EIS) improve outcomes for those with first episode psychosis, but larger trials may be needed. Pertinent evidence may be supplied by a full-scale RCT (Recovery After an Initial Schizophrenia Episode - RAISE), comparing two different ways of providing early treatment to people experiencing the early stages of schizophrenic disorders. As part of the RAISE trial, patients are currently being recruited at 34 study locations throughout the US to evaluate EIS including personalized medication treatment, individual resiliency training, supportive services, family psycho-education and education/ employment assistance (National Institute for Mental Health, *ongoing*).

Maintaining gains is a critical issue within the treatment of psychosis and few trials showed gains preserved beyond the treatment period - it may be that EIS are only effective while interventions are active (Birchwood and Fiorillo 2000). Research currently being conducted in the UK, the SuperEDEN (Sustaining Positive Engagement and Recovery) project, is following up a cohort of patients to examine outcomes after being discharged from services (UK Clinical Research Network, 2012).

Stroke

We found four systematic reviews focusing on stroke (Jones et al. 2010, Kwan et al. 2004, Lecouturier et al 2010a/b)

A lack of awareness of the warning signs of stroke or transient ischaemic attacks (TIA) leads to delays in seeking help by sufferers or witnesses. This lack of knowledge is seen at the same levels for stroke patients or those at risk of stroke as the general public.

Inappropriate action, as well as lack of recognition of symptoms, contributes to delays to hospital arrival, with the majority of patients phoning their GP rather than an ambulance.

Public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services.

Multi component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy.

There was no information about outcomes and the cost implications of late diagnosis.

Discussion of Recent Research

Recently, the Department of Health instigated a major 3 year communications campaign, *the FAST test:* Facial weakness, Arm weakness, Speech difficulties and Time to act fast, which commenced in February 2009 with the objective of enabling members of the public to recognise and identify the main symptoms of stroke and know that it needs to be treated as an emergency. The campaign used mass media including television, print, radio and the internet (Department of Health, 2009). An evaluation of the FAST campaign suggested that it performed well in terms of spontaneous and prompted recognition of the symptoms of stroke but that knowledge was highest following the second of five waves of the campaign, when spend was highest (TNS BMRB, 2010). Following the most recent advertising campaign in March 2012, an independent tracking survey among over 1800 adults, carried out by TNS BMRB, showed that the campaign was successful in increasing knowledge of stroke symptoms (any symptom:98%) and in improving awareness of the need to access services to the highest level seen so far at 74%. Higher scores were achieved by those aware of the FAST campaign and improvements were seen among key BME group also, (personal communication from Karen Pinder, Health Protection and Older People's Marketing Manager, Department of Health). An evaluation of stroke awareness campaigns conducted in England, Australia and Canada using pre- and post-campaign surveys found the greatest improvement in stroke awareness was created by the multifaceted FAST campaign, which had the greatest budget and reach (Trobbiani et al. *in press*).

Tuberculosis (Findings from systematic reviews)

Four systematic reviews examined late diagnosis and tuberculosis (Courtwright and Turner 2010, Liu et al. 2008, Sreeramareddy et al. 2009, Storla et al. 2008).

Statistically, there was no difference in time delays in low or high endemic countries, or low, middle, or high income countries.

The type of health care site and/or health practitioner that is initially accessed by patients seems to impact on the speed of diagnosis. Poverty, rural residence, being a woman, low awareness of tuberculosis and older age are associated with a greater risk of late diagnosis.

There was no information about the outcomes or cost implications of late diagnosis of tuberculosis within the included reviews.

There may be some merit in reminder systems to encourage return for results of tests, but more robust trials are needed.

Tuberculosis (Findings from UK primary studies)

Data on the prevalence of late diagnosis in the UK were limited. One study found that 50% of a small sample of patients prescribed antibiotics prior to confirmation of TB diagnosis experienced treatment delay. Another small study found that, of 62 patients with TB, only 4 out of 38 in-patients had been diagnosed prior to admission.

Being female, older, of white ethnicity or socio-economically deprived was associated with delays in the initiation of treatment.

Among White and UK born patients, shorter intervals were experienced by the most deprived. Recent migrants were less likely to experience delays, as were patients with pulmonary rather than extra-pulmonary disease.

Patient denial, delayed presentation and non-compliance were identified as barriers to diagnosis. Among GPs, a low index of suspicion, a lack of knowledge and sub-optimal clinical-patient communication were identified as barriers to diagnosis.

One small study investigating the utilization of healthcare resources by patients with TB demonstrated a very high rate of in-patient care, judged to be a consequence of the emergency admission of acutely ill, previously undiagnosed cases.

Both screening and case management support components of the London 'Find and Treat' outreach service for hard to reach patients with TB were found to be cost effective.

An educational programme resulted in the improved identification of active and latent tuberculosis, a higher percentage of new registrations screened for TB, and higher median numbers of tuberculin skin tests being carried out in intervention practices compared with controls.

Discussion

Where is late diagnosis of most concern?

There are four conditions were late diagnosis is of most concern: COPD, Dementia, HIV and Type 1 Diabetes.

COPD has a particularly high prevalence of late diagnosis, with an estimated 80% of cases remaining undiagnosed. Many of these cases are likely to be patients in the milder stages of the disease. Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009). Under-diagnosis was associated with costly hospital admissions for exacerbations of the condition.

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases, with doctors acknowledging their difficulties in distinguishing between dementia and 'normal ageing'. There was some ambivalence about diagnosing patients early

because both doctors and families of patients could not see therapeutic value in doing so.

There was evidence to suggest that a substantial proportion (16–51%) of children experience delayed diagnosis in type I diabetes (>24 hours for any reason).

Those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis, which has worrying implications with regard to onward transmission. Data from the Health Protection Agency indicates that 50% of new diagnoses are late in the UK.

There were some conditions where the lateness of the diagnosis had a considerable impact, such as chronic kidney disease and psychosis, leading to high morbidity and mortality, and less likelihood of remission or positive response to treatment. In these two cases, interventions such as early intervention services (psychosis) and decision support software for primary care staff (CKD) have improved the situation.

For myocardial infarction (STEMI) and stroke, the treatment available has improved considerably over the last decade and the health system has been re-organised to deliver the best care. However, patient delay remains an intractable problem and the mass media public awareness campaigns have not been as successful as hoped.

Who is most likely to experience late diagnosis?
Broadly, late diagnosis affects vulnerable groups such as older people or those living in poverty.

Age was identified as a barrier to early diagnosis in the included research. Older age was distinguished as a determinant of delay in the diagnosis of depression, tuberculosis and COPD. In contrast, younger age was found to be a barrier to diagnosis in those suffering from type 1 diabetes. Delayed diagnosis for older people might be a consequence of the increased presence of confounding co-morbidities in this age group. Alternatively, delayed diagnosis for older patients may be a result of beliefs held by doctors and patients that nothing can be done to halt progression (as was the case for dementia patients), that deterioration in health is to be expected as age increases, or simply of ageism.

Females were more likely to experience a delayed diagnosis of dementia, type I diabetes or tuberculosis.

A lower socio-economic status was implicated in delayed diagnosis both for type I diabetes and tuberculosis. Delayed diagnosis among less affluent populations may occur due to access difficulties or that fact that generally, less prosperous people demonstrate poorer health and are more likely to suffer from the co-morbidities which contribute to missed diagnoses. Low education levels were associated with delay in dementia, tuberculosis and type I diabetes.

Belonging to an ethnicity minority was associated with presenting with diabetic ketoacidosis at diagnosis of type I diabetes in children and young adults. White patients were more likely to experience delays in the treatment of tuberculosis

than ethnic minorities. Language barriers were mentioned by doctors when discussing communication problems with patients suffering from dementia.

Categorising delay

We found very little research examining administrative, organisational or procedural (system) determinants of diagnostic delay. System barriers to diagnosis require further investigation. Among this type of determinant, resource constraints and access issues were more frequently discussed than organisational/management issues. This may simply be a reflection of the fact that these factors are easier to record and investigate.

The Hansen model (Hansen et al. 2008) served as a useful starting point for categorising delay in order to create our systematic map. However, types of delay occurring for one condition may be specific to that condition, e.g. where symptoms are slow to appear. Any one model is bound to have limitations when trying to describe delays for the late diagnosis literature across all conditions. Ultimately, universal indicators for delays to diagnosis may be an unattainable goal due the disease-specific nature of delays within a particular condition.

It may be more useful to conceive of delays to diagnosis in terms of the length of intervals within the diagnostic process and factors impacting upon, or prolonging these intervals. However, with the exception of reviews which focused upon delays occurring in the diagnosis of tuberculosis (Sreeramareddy et al.2009, Storla et al. 2005) and myocardial infarction (Boersma et al 2006, De Luca 2008), the included reviews did not present any information with regard to specific time intervals within the diagnostic process. It may be that this practice is not sufficiently established to be described in systematic reviews as yet.

Patient delay

Patient delay was identified as barriers to prompt diagnosis and treatment for a number of conditions including chronic kidney disease, dementia, HIV, stroke, myocardial infarction, epilepsy and tuberculosis. Symptom misinterpretation and lack of knowledge were implicated in delayed presentation. In the case of epilepsy, the patient may be unaware of their condition until an attack is witnessed by another. Fear often appeared to influence patients' help-seeking behaviour.

Three of the four reviews concerning stroke concentrated on studies that described patient delay and its relationship with knowledge of the symptoms and warning signs of stroke. Lack of knowledge of the warning signs of a stroke or a TIA, as well as lack of action needed when a stroke is suspected, were found to be major determinants of delay. There was a similar finding for patients with STEMI.

Patient fear, denial, non-compliance with investigations and symptom misinterpretation were identified as barrier to prompt diagnosis and treatment of tuberculosis. Similarly, patients appeared to delay going to the doctor for fear of the stigma of mental illness associated with a diagnosis of dementia, and the subsequent loss of independence. Patients and their families may not recognise early symptoms of dementia, or may have got used to compensating for their relatives' cognitive deterioration. There was a perception that there were few

treatment options for dementia, so early diagnosis was not desirable. Low risk perception, fear of a positive diagnosis and fear of disclosure were all identified as barriers to HIV testing. Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid testing as a result of fear of a positive diagnosis. Fear of disclosure was a particular concern among African communities in the UK. Uptake of testing was inhibited among migrants who feared that HIV status might have a bearing on the immigration process.

It may be difficult to address patient delay, particularly where delays to help-seeking behaviour are influenced by fear (of disease or stigma). Where delay is caused by lack of knowledge, mass media campaigns can be employed to reduce symptom misinterpretation or delay in seeking appropriate help. However, such campaigns can be extremely costly and this review has not identified robust evidence of success. For stroke, public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services. For psychosis, the results of studies reporting on the impact of multi-focus awareness campaigns on reducing treatment delay were mixed and conflicting. With regard to myocardial infarction, the increased use of emergency services from public awareness campaigns has to be of concern as it places extra burdens on the health service and does not appear to result in significant gains to early diagnosis.

Doctor delay
Inadequate knowledge and training were identified as barriers to prompt diagnosis and treatment for chronic kidney disease, COPD, dementia and tuberculosis.

Diagnosing dementia in its early stages was judged to be difficult as symptoms were fluctuating and non-specific. Primary care providers wished to have more education about what constitutes 'normal ageing' so they were able to make accurate diagnoses. They expressed discomfort at using diagnostic tests and wanted greater support and input from specialist colleagues in secondary care. Lack of training in the use of spirometry contributed to the lack of confidence in using the equipment for the diagnosis of COPD. Spirometry was performed more often by those who were confident of interpreting the results. General practitioners' low index of suspicion, lack of knowledge and sub-optimal communication with patients were identified as barriers to the prompt diagnosis and treatment of tuberculosis. The improvement in identification of patients with tuberculosis, produced by a campaign to educate primary healthcare practitioners, suggests that it is possible to remedy deficits in clinical knowledge, although it may be difficult to replicate this success for other diseases or conditions in which a low index of suspicion is not a critical factor.

Communication difficulties were identified as barriers to diagnosis for chronic kidney disease, dementia, HIV and tuberculosis. Difficulties in disclosing and explaining a diagnosis of dementia were reported. Anxiety and reticence were also described among GPs reluctant to discuss HIV testing with patients (even in high-risk groups), which resulted in delays due to onward referral. Patients suggested

that GPs failed to adequately communicate the value of HIV testing. Finally, therapeutic nihilism was also exhibited by doctors, who were reluctant to initiate investigations as they were uncertain about what support might be available to dementia patients or what they might offer in support by way of treatment or services. In appears therefore, that factors over and above constraints to consultation time are impacting upon optimal communication between patients and clinicians.

System delay

The most frequently identified system determinants of delays to diagnosis were restricted access, insufficient consultation time and resources constraints. Access issues, in terms of geographical location or knowledge of availability of services, were described for chronic kidney disease, HIV and tuberculosis. GP workload and suboptimal continuity of care were identified as barriers to the prompt diagnosis and treatment of TB. Insufficient consultation time was also described as impeding diagnosis of dementia: the time of a typical visit to a doctor's surgery did not allow for the completion of diagnostic tests. Resource constraints also hindered the early detection of dementia. Doctors also felt discouraged by the low reimbursement for dementia care. There was evidence to suggest that the supply of primary care affects diagnostic rates for COPD. Key informants in the field of HIV and working with African communities in the UK noted that financial and human resources were often lacking in order to target African communities in the UK. Economic evaluations elucidating the cost-effectiveness of earlier diagnosis and treatment, should serve to identify where to direct resources in order to make best use of limited budgets.

Interventions

Early diagnosis of some conditions may be difficult to improve upon due to non-specific presentation (e.g. dementia) or due to aggressive onset of disease (e.g. type 1 diabetes). Nonetheless, having established whether or not those with a particular condition are likely to experience delayed diagnosis, and the effect that delayed diagnosis will have upon mortality and morbidity, the question immediately arises as to what can be done to promote early diagnosis and prompt treatment. Treatment delay may be considered equivalent to late intervention. However, an unmanageable quantity of literature was generated using terms to capture the concept of "early/late intervention" during the early stages of this review. Thus, literature was sought and examined only where "early/late intervention" and "treatment delay" occured alongside diagnosis terminology. Indeed, much of the literature examining early intervention is focused on the timing of treatment in relation to prognostic or clinical factors rather than undue or avoidable delay. Nevertheless, we must acknowledge that we may have failed to locate a proportion of the literature examining early intervention. Future research may help to identify this potential source of evidence.

For dementia, there was some evidence that doctor education improved the detection of the condition. However, the trials reviewed were not large and so could not present robust findings, and only one was conducted in the UK. An UK educational programme intended for primary care health professionals, resulted in

improved identification of active and latent tuberculosis and a higher percentage of new registrations screened for TB in those practices exposed to the intervention.

Multi-component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy for those suffering a stroke. However, public education campaigns were successful in increasing the knowledge of stroke symptoms, but not in improving the awareness of the need to access the emergency services. While the bulk of the literature focused upon delays within primary healthcare, we found relatively few studies examining mass media/patient education campaigns. This may be due to the expensive nature of such campaigns, or concerns about their efficacy or the longevity of their impact.

Specialised early intervention teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, the results with regard to interventions to reduce the duration of untreated psychosis were mixed and conflicting.

There was evidence to suggest that reminder systems produced shorter delays in tuberculosis diagnosis, but more substantive trials are required. Similarly, case finding strategies, targeted at high-risk groups may prove useful for identifying individuals with COPD and tuberculosis.

Medical advances in cardiology have been utilized by the health system to improve emergency care for patients suffering a heart attack. In the last decade, the re-organisation of services so that a majority of patients have rapid access to catheter laboratories and primary angioplasty, has resulted in lower mortality and morbidity for those patients who present in less than 6 hours from the onset of symptoms.

Costs
There was very little material about the cost implications of delayed diagnosis, but this may reflect a general dearth of economic data in the biomedical literature as a whole, and in systematic reviews in particular. Although authors of primary studies often report costs or cost-effectiveness, it is rarely the case that they provide data in a format which can be used within systematic reviews. Therefore, the presence of reliable cost-effectiveness data within reviews of reviews, including this one, is scant. Both Brown and Grimes (1995) and Dierick van Daele et al. (2008) have discussed the challenges in obtaining cost-effectiveness data for systematic review.

Economic evaluations need to weigh the initial increase in demand upon services that results from earlier diagnosis against savings attributable to avoiding the treatment of advanced disease, and the avoidance of losses due to individuals remaining socially and economically active. Where diseases are communicable, savings accrued from reduced transmission may be substantial – as has been suggested for HIV.

1. Background

Delayed diagnosis results in serious consequences for patients and healthcare professionals and has the potential to incur substantial financial costs. An analysis of incident monitoring in Australia suggests that up to 28% of adverse events in primary care pertain to diagnosis, with missed diagnoses (42%) being the most common diagnostic incident (Bhasale 1998). In a US study of 583 physician-reported diagnostic errors, 28% were judged to have caused death, permanent disability, or a near life-threatening event and 41% to have caused short-term morbidity, increased length of stay, or the need for higher level of care or an invasive procedure (Schiff et al. 2009).

There are numerous points at which a delay in diagnosis can occur:

- in the help-seeking behaviour of the patient
- access to healthcare (waiting for an appointment)
- clinical assessment in primary and secondary care (not investigating, missed diagnoses or misdiagnosing)
- test ordering (waiting for tests)
- test results (test results lost or misdirected)
- referral (referral waiting time, referral missed, prioritisation incorrect)

Hansen et al. (2008) delineate three categories of delay in diagnosis:

- 'patient delay' (that attributable to the patient)
- 'doctor delay' (that attributable to clinical staff)
- 'system delay' (that attributable to administrative and procedural errors)

There can also be time lost between diagnosis and referral to, or initiation of, treatment: 'treatment delay'.

In a systematic review of diagnostic error in primary care Kostopoulou et al. (2008) describe some common features of diagnostic difficulty including: atypical presentation, non-specific presentation, rarity of condition, presence of co-morbidity and perceptual features susceptible to subjective judgement. Determinants of delayed diagnosis other than clinical presentation have also been investigated. For example, three systematic reviews relating to the diagnosis of cancer have identified demographic factors associated with delayed diagnosis: socioeconomic status, age, gender and level of education (McDonald et al. 2006; Mitchell et al. 2008, Scott et al. 2006). Navaneethan et al. (2008) identify age, ethnicity and gender as factors influencing late referral in their systematic review of referral for chronic kidney disease. A systematic review of missed and delayed diagnosis of dementia (Bradford et al. 2009) identified educational level, age and marital status in association with delayed diagnosis.

A number of systematic reviews specific to a particular disease or condition and focusing upon late diagnosis have already been published. For example, there are

systematic reviews dealing with late diagnosis in primary care (Kostopoulou et al. 2008), cancer (McDonald et al. 2006, Scott et al. 2006), dementia (Koch and Iliffe 2010), stroke (Lecouturier et al. 2010) and tuberculosis (Sreeramareddy et al. 2009). However, to our knowledge no review has as yet been undertaken to systematically assess coverage of the evidence base across multiple conditions. This SREA serves to identify and characterise research in this area as well as highlighting any gaps in the evidence base.

In-depth review was then undertaken to determine how frequently late diagnosis occurs and whether it leads to increased costs in the NHS and in social care, those most affected by late diagnosis and its relationship with outcomes, and to identify interventions which reduce delays in diagnosis.

1.1 Definition of delayed diagnosis

Total delay in diagnosis may be simply dichotomised into two components: 'patient delay'- the time from onset of symptoms to first consultation with a healthcare provider, and 'health care system delay': the time from first health care seeking for diagnosis until diagnosis itself.

However, the following discussion of variability in the definitions of delay made by Storla et al. (1998) in their systematic review of diagnosis and treatment of tuberculosis, serves to highlight the practical problems involved in trying to define delayed diagnosis:

> *"Forty-nine studies defined onset as the debut of any symptom, two studies defined onset as debut of cough, and 1 study defined onset as debut of any pulmonary symptom. For six studies, a definition of symptom onset could not be obtained. With regard to definition of the first contact, 34 studies defined the first contact as the first visit to a qualified healthcare provider. However, some of these studies included "western medicine" provider within the category of a qualified healthcare provider; others used the time of first contact with the national TB program in defining the end of patient delay. Eighteen studies defined the first contact as the time when the patient sought contact with any healthcare provider outside the household, including traditional practitioners. Four studies recorded both. Six studies did not provide any information with regard to definition of the first contact."*

Similarly, studies vary widely with respect to their definitions of the end of delay. The end of delay can be considered variously as the time when: a correct diagnosis is made, when patients themselves are informed of the diagnosis, when patients are referred to secondary healthcare, when patients are referred to treatment and others will consider that delay has ended with the initiation of appropriate treatment. It is also the case that delayed diagnosis and its many components often remain undefined in studies.

We have therefore chosen the widest possible definition of delayed diagnosis in order to avoid any difficulties we might encounter in trying to exclude studies based on a cut-off point chosen somewhere between the extremes of 'onset of any

symptom' and 'initiation of appropriate treatment'. Using this approach allows us to reflect the approaches to late diagnosis which are presented in the evidence base rather than imposing a framework upon it a priori.

For the purposes of this review late/delayed diagnosis will be defined as:

Any delay (total, patient, primary care, secondary care, or any combination of delay types), described at any point within the diagnostic pathway between initiation of any symptom in the patient and initiation of appropriate treatment.

1.2 Models of delayed diagnosis

The Andersen model of delayed diagnosis has been widely adopted in the literature (Walter et al. 2011). However, we have avoided using the model developed by Andersen et al. (1995), or the refinement of this model described by Walter et al. (2011) because in both models the emphasis is upon patient delay rather than health-care system delay.

As discussed in the National Patient Safety Agency's thematic review of delayed diagnosis of cancer: "… research has tended to focus on delays attributable to patients and, as a result, delay is often ascribed to patients because that is where there is evidence. Yet this conclusion may be an artefact of the research focus; delays further along the pathway are likely to be significant, have been underestimated and under researched." (NPSA 2010)

Wahls (2007) reports that almost 65% of diagnostic errors have an important contribution of system errors, of which many are test results lost to follow-up, i.e. missed results. Following a survey of primary care providers, Wahls and Cram (2007) concluded that missed results leading to clinically important treatment delays are an important and likely underappreciated source of diagnostic error.

Indeed, Evans et al. (2006) found that the Andersen et al. model was inadequate to encompass the events as described by patients which led to delayed diagnosis. They found it necessary to expand upon the model in order to capture common delays attributable at least in part to a doctor or the health care system, such as the non-investigation of symptoms, treatment for the wrong condition, lack of follow-up, referral delays and system delays.

We have adopted the model developed by Hansen and colleagues, as shown in Figure 1, in which various components of delay in diagnosis have been assigned to three broad categories: 'patient delay', 'doctor delay' and 'system delay' (Hansen et al. 2008).

Figure 1: Hansen model for the categorisation of delays in diagnosis (Hansen et al. 2008)
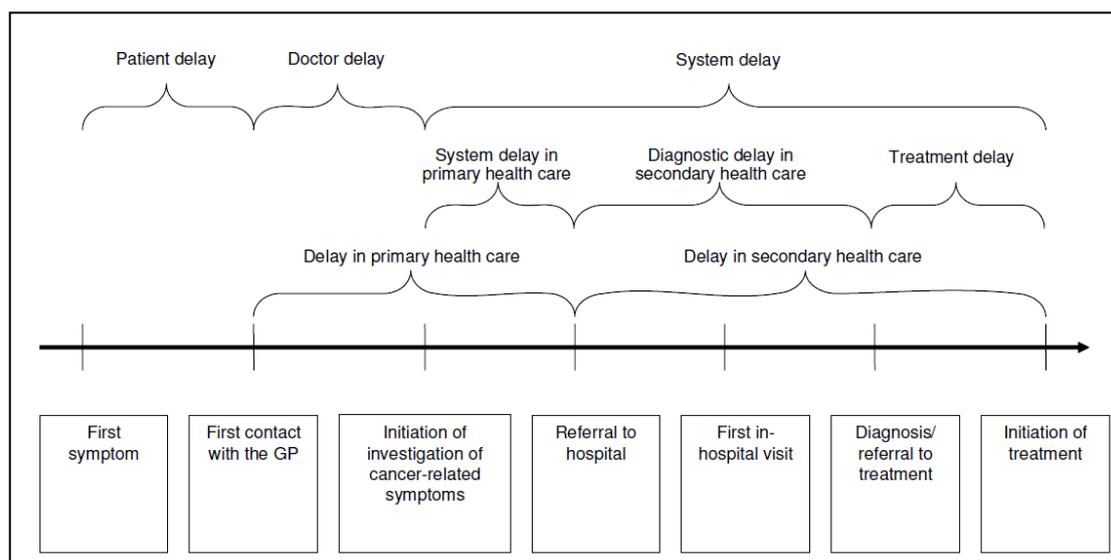
Patient delay is defined as any delay from the onset of a symptom to first contact with a GP.

Doctor delay is defined as primary care practitioner delay.

System delay is primarily regarded as hospital or secondary care delay and is further subdivided into system delay in primary care, diagnostic delay in secondary healthcare and 'treatment delay' – the interval between diagnosis and referral to, or initiation of, appropriate treatment.

1.3 Review questions

Part I of the systematic review, used to construct a systematic map of the evidence base, is driven by the following research question:

> *What is the nature and extent of UK evidence on delayed diagnosis?*

Part II of the systematic review, which focuses upon a limited number of conditions, namely chronic kidney disease, dementia, type I diabetes, tuberculosis and chronic obstructive pulmonary disease, is used to examine and synthesise the findings of suitable studies:

In-depth questions determined in consultation with research and policy advisors:

1. *What is the prevalence of late diagnosis?*
2. *What are the determinants of late diagnosis?*
3. *What are the outcomes of late diagnosis?*
4. *What are the cost implications of late diagnosis?*
5. *Which interventions reduce delays in diagnosis?*

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2. Aims and methods

2.1 Aims

This systematic rapid evidence assessment (SREA) is intended to bring together the evidence base in order to understand the nature and extent of UK evidence on delayed diagnosis. It uses data from systematic reviews of late diagnosis relating to specific diseases and conditions, synthesising information from studies conducted abroad and in the UK. Where reviews were not available, primary studies conducted in the UK were synthesised.

This report presents a systematic map of the research evidence relevant to answering the mapping question '*What is the nature and extent of UK evidence on delayed diagnosis?*'

A two-stage systematic review was conducted:

    (i) A systematic rapid evidence assessment resulting in a descriptive mapping exercise and a quality assessment of systematic reviews;

    (ii) An in-depth review and synthesis of the findings of 12 systematic reviews and 11 primary studies.

The map was discussed in consultation with relevant researchers and the policy customer. This consultation was used to inform a decision about policy relevant topics for in-depth review based on the available evidence.

Eleven conditions were selected for in-depth review:

- Chronic Kidney Disease (CKD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Dementia
- Depression
- Type I Diabetes
- Epilepsy
- HIV
- Myocarial Infarction
- Psychosis
- Stroke
- Tuberculosis (TB)

All of these conditions had been subject to systematic review with the exception of COPD, and epilepsy where we collated data from UK primary studies. The systematic reviews relating to tuberculosis were deemed to have limited relevance to the UK healthcare system and therefore a synthesis of UK primary studies was also conducted.

In order to understand more fully the issue of late diagnosis, answers to the following sub-questions were sought:

1 *What is the prevalence of late diagnosis?*
2 *What are the determinants of late diagnosis?*
3 *What are the outcomes of late diagnosis?*
4 *What are the cost implications of late diagnosis?*
5 *Which interventions reduce delays in diagnosis?*

2.2 Review type

This systematic review is a Systematic Rapid Evidence Assessment (SREA). It is a focused review with a limited search. The limited time scale of the project and large body of literature required that the scope was curtailed in the following ways:

(i) Evidence other than systematic reviews was restricted to that available for the UK.

(ii) Evidence was restricted to that available within the last 10 years.

(iii) Evidence was restricted to that not concerning cancer.

(iv) A specific as opposed to sensitive search strategy was developed which employed a comprehensive rather than exhaustive search strategy.

(v) Search sources were limited to bibliographic databases and reference lists of key papers. National Clinical Directors were contacted internally for their input and asked to contribute relevant studies. Hand searching of key journals, web-site searching, and a search of grey literature were not conducted.

Although not a full systematic review, EPPI-Centre tools and guidelines were used throughout the review in a transparent and systematic fashion in order to limit bias.

2.3 Identifying and describing studies

2.3.1 Criteria for considering reviews
To be included in the systematic review, research evidence had to meet the following criteria:

- Focus: late diagnosis is a central component of the study.
- Research design: primary study conducted in the UK/ systematic reviews
- Publication date: study published from 2001 onwards.
- Language: study available in English.

We excluded those studies which:

- Described the characteristics, traits or relative merit of diagnostic tools.
- Investigated mass screening interventions, (studies that described case finding for at risk groups, e.g. for pulmonary disease, were included).
- Focussed upon cancer or malignancies.

- Had no abstract (or too little information in the abstract to include the study).

Inclusion criteria for studies were first applied to titles and abstracts identified during searching. Where no abstract was available from bibliographic records, attempts were made to retrieve the abstract online: if unsuccessful the study was excluded from the review. A list of those studies excluded because they did not have an abstract or because we were unable to retrieve them in the time available, is available from the authors upon request.

As primary prevention measures have already been relatively well studied and incorporated into national policy, the focus of this review is on earlier diagnosis of disease following the onset of symptoms rather than the identification of risk factors for primary prevention.

Rationale for eligibility criteria:

- UK-only evidence
    - o the inclusion of systematic reviews within the SREA allowed international evidence to be captured without generating an unfeasibly large number of studies and thus extending the limited time scale of the project;
    - o the decision to restrict included primary studies to those conducted in the UK will ensure that information most relevant to policy and practice in the UK is retrieved.
- 10 year date limit
    - o preliminary searches indicated that the literature on late diagnosis was too extensive to complete the review in the time allocated without a date limit;
    - o studies published before this period are less likely to be relevant to current policy and practice and may have been superseded by more recent studies.
- *English language studies* - the decision to restrict to English language studies was pragmatic and reflects a lack of resources for the translation of non-English language papers. Papers pertinent to the UK are also unlikely to be written in a language other than English.
- *Cancer* - studies focusing upon cancer or malignancies are not included because there is already a substantial amount of research and related policy activity on improving early diagnosis of cancer.

2.3.2 Search Sources
Bibliographic databases: the following bibliographic databases were searched for pertinent systematic reviews/primary research:

- British Nursing Index (BNI)
- CINAHL (Cumulative Index to Nursing and Allied Health)
- Cochrane Library of Systematic Reviews
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effectiveness)

- Health Technology Assessments (HTA)
- NEED (NHS Economic Evaluation Database)
- HMIC (Health Management Information Consortium)
- PSYCHINFO (Behavioural sciences and mental health literature)
- PUBMED (Biomedical literature)

Citation checking: references from relevant reviews identified during searching were screened to identify further papers.

Requests to expert informants: National Clinical Directors were contacted internally for their input and asked to contribute relevant studies.

2.3.3 Search Strategy
A comprehensive search strategy was developed using combinations of controlled vocabulary and free-text terms (the latter restricted to the title or abstract fields). Results of preliminary searches and text-mining technology were used to improve the use of relevant free-text terms and controlled vocabulary to describe key concepts.

The search strategies applied to different bibliographic databases are presented in Appendix 1.

Treatment delay may be considered equivalent to late intervention. However, preliminary test searches indicated that an unfeasible amount of literature was generated by conducting a search using terms to capture the concept of "early/late intervention". Therefore, "early intervention" was used as a search term only in the psycINFO database to capture psychiatric literature where "early intervention" is used to denote a prevalent issue in the diagnosis and treatment delay encountered in a number of psychiatric conditions. Otherwise, literature was sought and examined where "early/late intervention" and "treatment delay" occured alongside diagnosis terminology: i.e. where early intervention and treatment delay were discussed alongside diagnosis, in the context of diagnosis, or where the interval between diagnosis and treatment was explicitly described.

2.3.4 Screening
Once an inter-rater reliability (98%) and a baseline inclusion rate were established (based on a random sample of approximately 350 studies), we conducted a power calculation to determine the sample size required to generate reviewer terms to be employed in a text-mining facility. Over 3,800 studies were screened to identify terms indicative of included and excluded studies. The text-mining facility within EPPI-Reviewer 4 was then employed to prioritise studies for screening.

When the inclusion rate of the prioritised studies dropped to 0.5%, we ceased screening studies. A total of 18,075 (70%) of the 25,783 unique records were screened on title and abstract.

2.4 Quality assessment, data extraction and synthesis

2.4.1 Quality assessment
To quality assess the systematic reviews, we retrieved the full papers. Using the AMSTAR critical appraisal tool (Shea et al. 2007), the papers were graded on:

- the existence of an a priori design;
- the comprehensiveness of the searching;
- whether studies were selected and data extracted by two reviewers;
- whether there was information about included and excluded studies;
- whether the studies had been quality assessed and if that assessment had informed the findings;
- robustness of methods used to combine the findings;
- whether an assessment of publication bias had been made.

Quality assessment was conducted separately by two reviewers who then met to compare findings. Disagreements were resolved through discussion and the arbitration of a third party where required.

We assessed primary studies using the QATSO critical appraisal tool (Wong et al. 2008) and for studies using a comparison group design, we used an appraisal tool developed for the EPPI-Centre (Shepherd et al. 2003).

The QATSO tool was used to grade studies as being of high, medium or low quality based on:

- rigour of sampling;
- whether independent and dependent variables were reliably measured;
- response rate;
- whether there was adjustment for confounding;
- confidence in statistical measures used.

Additionally, the tool assessing the outcome evaluations with a comparison group included criteria examining three key biases: selection bias (whether the two groups, intervention and control, were equal in terms of major prognostic factors), attrition bias (the attrition rate should be less than 30% overall), and outcome reporting bias (outcomes should be reported for all groups).

Qualitative studies were assessed using criteria developed and used in previous EPPI-Centre reviews (Rees et al 2009) and informed by principles of good practice for conducting social research with the public (Harden et al 2004).

The quality assessment tools used to critically appraise the studies in this review are presented in Appendix 2.

2.4.2 Data extraction

Mapping
For the purposes of constructing the systematic map we described the characteristics of the included studies on the basis of information found in the

abstract. A standardised framework, developed specifically for this review, was used to extract and record information from each review.

Each study was described according to:

- the disease or condition examined;
- the type of delay (using the typology of Hansen et al. 2008 – see section 1.2);
- the type of study designs contained in the review;
- type of intervention if applicable;
- determinants of delay, including demographic, medical (from Kostopoulou et al. 2008), and system, patient beliefs, knowledge and attitudes, and patient / provider communication;
- outcomes of diagnostic delay;
- outcomes of interventions to reduce delay;
- the number of participants in the study.

Although most of the abstracts did not cover all the information, there was enough material to guide policy makers at the Department of Health, regarding decisions about the focus of the in-depth review.

In-depth review

For the purposes of the in-depth review, we extracted data from the included studies using the full-text of each paper. A standardised framework, developed specifically for this review, was used to extract and record information from each review.

For each systematic review the following information was extracted:

- the number of included primary studies;
- the pooled number of participants within the review;
- countries of origin of primary studies;
- demographic and other characteristics of the population under study;
- definitions of disease states and conditions;
- data regarding the prevalence, determinants, outcomes and costs of delayed diagnosis, and characteristics and outcomes of any interventions intended to reduce delays in diagnosis.

For each primary study the following information was extracted:

- research design;
- number of participants;
- demographic and other characteristics of the population under study;
- definitions of disease states and conditions;
- data regarding the prevalence, determinants, outcomes and costs of delayed diagnosis, and characteristics and outcomes of any interventions intended to reduce delays in diagnosis.

2.4.3 Synthesis

The findings from reviews were grouped by disease state/ condition and thereafter, successive syntheses are presented collating data regarding prevalence, determinants, outcomes, costs and interventions respectively. Where possible, syntheses present review authors' pooling of data. Often, authors had presented findings in narrative (i.e. without a statistical meta-analysis) form and, as such, the syntheses of this rapid review are themselves narrative in form.

Each chapter was reviewed by relevant National Clinical Directors and colleagues prior to the final draft being written. Where their feedback concerned the systematic review evidence, this was incorporated directly into the syntheses; where the material went beyond the evidence supplied by the reviews (or primary studies for COPD, epilepsy and tuberculosis) and gave, for example, information that was more up to date or particularly relevant to the UK context, this was included in the 'discussion' section for each chapter.

2.5 References

Hansen R, Olesen F, Sørensen H (2008) Socioeconomic patient characteristics predict delay in cancer diagnosis: A Danish cohort study. *BMC Health Services Research* 8: 49

Harden A, Garcia J, Oliver S, Rees R, Shepherd J, Brunton G, Oakley A (2004). Applying systematic review methods to studies of people's views: an example from public health research. *Journal of Epidemiology and Community Health*, **58**: 794-800.

Rees R, Oliver K, Woodman J, Thomas J (2009). *Children's views about obesity, body size, shape and weight: a systematic review*. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London.

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* **7**:10

Shepherd J, White I, Rees R, Thomas J, Brunton G, Harden A, Kavanagh J, Sutcliffe K, Oliver S, Oakley A (2003). *A systematic comparison of different sets of quality assessment criteria in systematic reviews of effectiveness in health promotion*. Paper presented at XI Cochrane Colloquium, Barcelona, 26-31 October.

Wong W, Cheung C, Hart G (2008) Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. *Emerging themes in Epidemiology* 5: 23-26

3. Results

3.1 Study Selection

The search of bibliographic databases provided a total of 28,994 citations. Sixty-seven papers were identified via experts and reference checking. After removing duplicate references, 25,799 records remained. Using text mining tools, we prioritised 18,075 (70%) records for screening. Of these, 16,818 were excluded after reviewing the abstracts because it was judged that they did not meet the eligibility criteria. Two additional studies were excluded because it was not possible to retrieve the full text of the study within the timeframe of the review.

We identified 43 systematic reviews investigating late diagnosis. UK primary studies investigating late diagnosis numbered 606, of which 11 investigated late diagnosis and COPD, 12 investigated late diagnosis and tuberculosis and 4 investigated late diagnosis and epilepsy.

A flow diagram illustrating the process of study selection throughout the review is presented in Figure 2 below.

3.2 Systematic map

Studies were coded on abstract only to enable decision-making about the focus of the in-depth review. When we data extracted the full paper, additional information altered the final coding and some studies were excluded, and we found or were given reviews later in the process. However, we present data from the initial coding here to give an overview of research in this area.

There were 35 systematic reviews that examined late diagnosis and specific conditions, the remaining nine looked at the phenomenon of late diagnosis across conditions or in a particular area of health care. The majority of the reviews were published in the last four years. Most of the reviews (n=22) included primary studies that were observational studies.

The research was focused on prevalence (systematic reviews n=19, COPD n=6). Trials or interventions to reduce delay were examined in 15 systematic reviews and four primary studies focussing upon COPD. Determinants of delay were examined in 28 studies (systematic reviews n=25, COPD n=3), but only three studies presented information on the cost implications of delay.

Delay was concentrated in primary healthcare (n=29): doctor delay (n=22) and patient delay (n=21), with very few studies mentioning delay in secondary healthcare (n=5).

Tables detailing the coverage of types of conditions, date of publication, study design, number of participants, types of delay and studies addressing each of the review's five sub-questions relating to prevalence, determinants, outcomes, costs and interventions to reduce delayed diagnosis, are presented in Appendix 3.

3.3 Quality Assessment

The overall AMSTAR quality score for each systematic review is presented in Table A4.1 in Appendix 4.

Scores ranged between 3/11 and 11/11. Seven reviews had an AMSTAR score of 3-5, twelve reviews had a score of 6-8 and 24 reviews had a score of 9-11.

After application of the AMSTAR quality assessment tool (see Appendix 2) for assessment of the methodological rigour of the included reviews, a record was made of whether criteria 3, 6 and 7 were satisfied i.e. comprehensive literature review conducted (criterion 3), characteristics of included studies provided (criterion 6), scientific quality of the included primary studies assessed (criterion 7). It was our original intention to apply a minimum quality threshold to our review such that systematic reviews not having fulfilled all 3 criteria would be excluded.

However, in applying this quality threshold we would have excluded more than half the studies from our review. While 37 of the 43 reviews undertook a comprehensive literature search, only 28 reviews assessed the scientific quality of the included primary studies. Therefore, in order to maximise data available for synthesis and promote coverage of the widest possible range of conditions, we have not applied a minimum quality threshold in this instance. The AMSTAR scores of studies which satisfied the three-point, minimum quality threshold are marked with an asterix within the characteristics of included studies tables.

For primary studies examining late diagnosis of chronic obstructive pulmonary disease, four of the primary studies, appraised using the QATSO tool, were graded high, and seven medium. Seamark et al. (2001) failed to avoid selection and attrition biases, scoring low on the trustworthiness criterion; therefore it was excluded from this review. Full details of the QATSO scores are provided in table A4.2 in Appendix 4.

Of the four primary studies examining late diagnosis of epilepsy, appraised using the QATSO tool (see Appendix A2.2), all were graded medium quality. Full details of the QATSO scores are provided in table A4.4 in Appendix 4.

Of the primary studies examining late diagnosis and tuberculosis, appraised using the QATSO tool (see Appendix A2.2), two were graded medium and seven high. Full details of the QATSO scores are provided in table A4.5. Griffiths et al. (2007), appraised using the quality assessment tool for comparison group studies, was judged to be of high quality (see Appendix A4.6). Two qualitative studies (Metcalf et al. 2007, Nnoaham et al. 2006), were judged to be of medium quality (see Appendix A4.7).

Figure 2: Flow of studies through the review

Records identified through
database searches
n = 28994

Records identified through
other sources
n = 67

Records after duplicates removed
n = 25799

Records prioritized via text
mining facility and screened on
title and abstract
n = 18075

Records excluded on
title and abstract
n = 16818

- Pre-2001 n=3
- Not English language n=213
- Not UK (primary studies only)
  n=5856
- Cancer studies n=26
- Diagnostic accuracy studies n=914
- Not late diagnosis n=6203
- No abstract n=245
- Screening studies n=119
- Not empirical research
  (primary studies only) n=3237
- Not available in time n=2

Included Studies
n = 1257

- Case Reports n=540
- Systematic reviews (case
  series) n=16
- Primary Studies n=606
- Linked studies n=11

- **Systematic reviews n=43**
- **COPD primary studies n=11**
- **TB primary studies n=12**
- **Epilepsy primary studies n=4**

4. Chronic Kidney Disease

Late diagnosis of chronic kidney disease (CKD) increases the risks of patients suffering from the consequences of untreated disease, including progression towards established renal failure with attendant need for renal replacement therapy and risk of premature death.

Late referral to renal care and unplanned starts on dialysis may be associated with worse outcomes including: higher mortality and morbidity, a reduced chance for preparation for dialysis, an increased chance of infection resulting from temporary vascular access catheters, a reduced chance of receiving optimal treatment and increased costs.

There was little consensus as to what constitutes 'late referral'. Late and early referrals were variously defined in individual studies. Please see Table 4.1 for a summary of the different categories of late and early referral within the included reviews.

4.1 Overall summary of findings

The proportion of referrals occurring within four months of the need to start dialysis ranged from between 20% and 50%. Two primary studies found evidence to suggest that approximately 40% of late referrals were attributable to patient non-compliance with appointments.

There was no evidence that gender and ethnicity were associated with late referral for chronic kidney disease. It was unclear whether age, socio-economic status, co-morbidities or geographical barriers to access influenced the timing of referral.

Doctors' lack of knowledge and awareness of guidelines, inadequate training and faulty communication between primary care doctors and nephrologists were identified as barriers to early referral.

Late referral resulted in unfavourable outcomes: significantly increased mortality; a prolongation of initial hospital stay; lower uptake of peritoneal dialysis; permanent access was less likely and temporary access more likely; erythropoietin usage was lower; and serum creatinine levels were higher and haemoglobin levels were lower as compared with patients referred early to nephrology care.

There is evidence to suggest that earlier referral is associated with lower costs.

4.2 Included studies

We found five systematic reviews relating to delayed referral in CKD (Black et al. 2010; Chan et al. 2007, Kahn and Amedia 2008, Navaneethan et al. 2008, Smart and Titus 2011).

Three of the reviews examined outcomes resulting from late, as opposed to early referral for those with CKD (Black et al. 2010, Chan et al. 2007, Smart and Titus 2011).

The systematic review by Black et al. (2010) included an examination of the clinical effectiveness of, and barriers to, early referral. Black and colleagues also examined the cost-effectiveness of early referral strategies for management of people with renal disease and the impact of later referral upon health outcomes.

The meta-analysis by Chan et al. (2007) pooled results from 22 studies to compare differences in mortality and duration of hospitalization in patients with CKD referred early versus late to nephrologists.

Similarly, Smart and Titus (2011) produced a systematic review with meta-analyses examining outcomes of early versus late nephrology referral in CKD.

The review by Kahn and Amedia (2008) had the stated aim of defining cost of care and evaluating interventions to delay progression and improve outcomes in CKD.

Finally, Navaneethan et al. (2008) reported a systematic review of patient and health system characteristics associated with late referral in CKD.

In their examination of factors influencing early referral, Black et al. (2010) included all of the studies appearing within the review by Navaneethan et al. (2008), plus an additional five studies. Therefore, we review only the results reported by Black et al. (2010). The characteristics of all five reviews are presented in Table 4.1 below.

Number of contributing reviews: 4

4.3 Prevalence

Black et al. (2010) included five studies reporting that the proportion of referrals occurring within four months of the need to start dialysis ranged between 20 and 50% (Lamiere and Van 1999, Nakamura 1997, Roderick et al. 2002, Levin 2000, Obrador and Pereira 1998).

Black et al. (2010) included two studies reporting that 42% of late referrals could be attributed to patient non-compliance (Jungers et al. 1993, Sprangers et al. 2006).However, Navaneethan et al. (2008) noted that in the former of these studies, the role of patient non-compliance could not be adequately assessed as most studies identified late referral of patients from dialysis records.

One retrospective observational study of 1391 French patients included within Kahn and Amedia (2008) found that only 30% of patients received nephrological care six months before dialysis initiation. This figure did not change significantly in over a decade, from 1989-2000 (Jungers et al. 2006).

Table 4.1: Characteristics of included reviews: Chronic Kidney Disease (CKD)

Systematic review [AMSTAR score]	Number of primary studies within systematic review	Pooled number of participants	Countries	Participants	Disease State/ Condition (CKD; Early and Late Referral)
Black et al. (2010)* [10/11]*	*Is early referral for CKD clinically effective?* 7 studies: Prospective cohort studies (2) Retrospective cohort studies (5)	114,073	US (3) France (2) Mexico (1) UK (1)	3 studies recruited consecutive patients with end stage renal disease (ESRD). 3 studies excluded those with acute renal disease (ARD). 2 studies excluded those < 18 yrs old. 2 studies excluded those returning to dialysis following failed transplant. Males exceeded females in all studies, (range 51% - 100%).	<u>CKD stages</u> - Stage 1 Kidney damage with normal or raised GFR (. 90 ml/min/1.73 m2) - Stage 2 Kidney damage with mildly impaired GFR (60.89 ml/min/1.73 m2) - Stage 3 Moderately impaired GFR (30.59 ml/min/1.73 m2) - Stage 4 Severely impaired GFR (15.29 ml/min/1.73 m2) - Stage 5 End-stage renal failure or GFR (< 15 ml/min/1.73 m2) Few of the studies reported information about the stage of CKD at key time points, i.e. first diagnosis or first referral to a specialist. <u>Early/Late Referral</u> Definitions of "early" based on time from dialysis (> 12 months) or severity (stage 3–4 disease).

Systematic review [AMSTAR score]	Number of primary studies within systematic review	Pooled number of participants	Countries	Participants	Disease State/ Condition (CKD; Early and Late Referral)
Black et al. (2010) contd…	*Does late referral for CKD impact upon health outcomes?* 17 retrospective cohort studies	16,600	UK (3) USA (3) Taiwan (3) Australia and NZ (1) Austria (1) Brazil (1) France (1) Germany (1) Japan (1) Korea (1) Norway (1)	All studies recruited patients to their study at the time of initiation of dialysis/ renal replacement therapy (RRT).	Early/Late Referral In the 17 studies, very late referral was compared, in most cases, with referral that was 1–6 months before the initiation of dialysis or RRT.
Chan et al. (2007)* [10/11]*	22 studies: Prospective cohort studies (3) Retrospective cohort studies (19)	12,749	UK (7) US (5) France (3) Austria (1) Belgium (1) Brazil (1) Italy (1) Norway(1) Taiwan (1) Turkey (1)	End stage renal disease (ESRD) patients. Average age 55.6 yrs (weighted by inverse variance). Males 57.3% (weighted for sample size).	CKD /End Stage Renal Disease Undefined. Early/Late Referral Late versus early referred patients, as defined in individual studies: "The definition of timing varied from study to study."
Kahn and Amedia (2008) [3/11]	Unclear	Unclear	Not reported	Kidney disease patients on dialysis or with end stage kidney disease.	CKD /End Stage Renal Disease Undefined.

Systematic review [AMSTAR score]	Number of primary studies within systematic review	Pooled number of participants	Countries	Participants	Disease State/ Condition (CKD; Early and Late Referral)
Navaneethan et al. (2008) [10/11]	18 studies: Prospective cohort studies (2) Retrospective studies (12) Physician surveys (4)	10,115 patients; 1321 physicians	Patients: US(7) UK (3) Australia and NZ (1) Europe (1) France (1) Physicians: UK (2) Canada (1) Europe (1)	Patients ≥ 18 yrs old. Included studies varied in exclusion vs. inclusion of patients who had "inevitable" late referral (i.e. patients with an acute cause of ESRD without opportunity for timely evaluation by a specialist.	CKD /End Stage Renal Disease Undefined. Late Referral Months prior to start of dialysis or stage of CKD: <6 months (2 studies) < 4 months (2 studies) < 3 months (4 studies) <1 month (3 studies) Creatinine >4mg/dl (1 study)
Smart and Titus (2011) [9/11]	27 studies: Prospective cohort studies (4) Retrospective cohort studies (21) Database analyses (2)	17,646: 11,734 referred early; 5912 (33%) referred late	US (5) France (4) Spain (4) UK (3) Europe (2) Italy (2) Australia (1) Canada (1) Japan (1) Korea (1) Norway (1) Taiwan (1) Turkey (1)	Patients ≥ 18 yrs old. Studies involving participants with acute renal failure excluded.	CKD Undefined. Late Referral Early and late referral defined in terms of the time period between specialist nephrology referral and starting dialysis. Studies using estimated glomerular filtration rate for defining early and late referral, were excluded.
Those studies marked with an asterix satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool (see Appendix 2).					

4.4 Determinants

Two reviews contributed to our understanding of the determinants of late referral, Black et al. (2010) and Navaneethan et al. (2008) Navaneethan and colleagues reviewed the evidence on patient and health system characteristics associated with late referral. However, in their examination of factors influencing early referral, Black et al. (2010) included all of the studies appearing within the review by Navaneethan et al. (2008), plus an additional five studies. Therefore, we review only the results reported by Black et al. (2010). We have not included data relating to insurance status as this is not directly relevant to the UK healthcare system.

Each determinant is accompanied by the number of contributing studies (n) and where possible, we have noted positive (+), negative (-), or no (□) association with late referral. Associations with risk of delayed referral are statistically significant unless indicated non-significant (NS).

The determinants of late referral for CKD are presented in Table 4.2 below.

Table 4.2: Determinants of late referral for Chronic Kidney Disease (CKD)

Determinants	Black et al. (2010) No. of primary studies (n); Association with late referral: Positive + (late referral more likely); Negative –(late referral less likely) ; None □.(no association with late referral)
Demographic	**Age (4+)(4□)** Older age (3+)(4□); Physicians less likely to refer older patients (1+) **Gender (1-) (3□)** Male (1-NS) (3□) **Ethnicity** Not black or white(1+); Black and Hispanic (2+); White British (1+NS); Ethnicity (3□) **Lower Socio-economic Status** Late referrals higher in areas of greater social disadvantage (1, Australia); Less affluent populations referred earlier (1, Northern Ireland); Homeless/unemployed (1+, USA); Education (1□, USA);
Medical	**Co-morbidities (5+)(1-)(2□)** Higher Index of Co-existent Disease score (1+); Active cancer (1+); Co-existing illness (1+); Co-morbidity (1+)(2□); Higher Charlson Co-morbidity Index (1+); Hypertension/ Malignancy/ Coronary Artery Disease/ Diabetes (1-)

Determinants	Black et al. (2010) No. of primary studies (n); Association with late referral: Positive + (late referral more likely); Negative –(late referral less likely) ; None □.(no association with late referral)
	Etiology Non-diabetic kidney disease (1+); Congenital kidney disease patients referred earlier than hypertensive (1); Rapidly progressing kidney disease (1+)
System	**Access to health care (geographical barriers)** Large city centres (1+, 3 European regions); Rural >1hr from dialysis units (1□, US); Further from renal centre (1+, Northern Ireland); Correlation late referral and distance to dialysis centre (1, Australia)
Knowledge, beliefs and attitudes of patients	Patient non-compliance accounts for 42% referrals (2)
Knowledge, beliefs and attitudes of health care professionals	Physicians less likely to refer older patients (1+) Hospital doctors more likely to refer to nephrologist than GP (3); Non-specialists worse at identifying stage 3 or 4 CKD (1); Non-specialists less likely to refer to/request input from nephrologist (1); Non-specialists less likely to be aware of practice guidelines (1); Non-specialists less likely to refer non-symptomatic patients (1); Increasing complex clinical scenarios (1); Physician rationing influenced by age, co-morbidities, distance to/ overcrowding of, dialysis centres (1); Referring physicians' fear of negative evaluation by nephrologists (1); Lack of specific referral criteria for end stage renal disease (1); Referring physicians (>90%) judge training regarding timing or indication for referral for CKD inadequate (1)
Communication barriers	Lack of/ faulty communication between primary care doctors and nephrologists (1)

Determinants: Key Findings

Demographic

- Older age: results were mixed and conflicting, with 4 studies suggesting older age is associated with late referral for CKD and 4 studies finding no association.

- Gender: no significant association was found between gender and referral timing for CKD.

- Ethnicity: results were conflicting, the majority of studies found no association between ethnicity and referral timing for CKD.

- Socio-economic status: 1 UK study found that less affluent populations were referred earlier, 2 studies found evidence to suggest late referral was more likely with lower socio-economic status.

Medical

- Co-morbidities: Five studies found that late referrals were more likely with co-morbidities. Two studies failed to find an association between co-existing illness and late referral for CKD. One study found that patients with hypertension, malignancy, coronary artery disease and diabetes were less likely to be referred late, which possibly due to the fact that these patients have more interaction with doctors and are more closely monitored than others.

- Etiology: Patients with non-diabetic kidney disease and rapidly progressing kidney disease were more likely to be referred late. Congenital kidney disease patients were referred earlier than those with hypertensive kidney disease.

System

- Access (geographical barriers): The majority of studies suggested that late referral was more likely where patients were located in rural areas and further from specialist facilities. Conversely, one survey of a cohort of incident dialysis patients in three European regions found that late referral was more frequent in large city centres than regional centres.

Knowledge, beliefs and attitudes

- Patient non-compliance: compliance with appointments was identified as an important issue in two studies where approximately 40% of late referrals were attributed to this factor.

- Physicians: non-specialist and primary care physicians were less likely to refer patients early, less likely to refer non-symptomatic patients, less able to identify stage 3 and 4 CKD than specialists and one study found that over 90% of referring physicians judged that their training regarding timing or indication for referral for CKD was inadequate. A Canadian study found that physicians' decisions to refer were influenced by age, co-morbidities and distance to and overcrowding of dialysis centres.

Communication barriers

- Lack of communication and faulty communication between primary care doctors and nephrologists were identified as determinants of late referral.

4.5 Outcomes

Numerous outcomes were examined for different groups according to referral timing in the included systematic reviews. We make a report here of the outcomes common to more than one review to highlight those outcomes for which the evidence is most prominent: mortality, duration of initial hospitalisation, access to

peritoneal dialysis, placement of vascular access, use of erythropoietin and finally, creatinine and haemoglobin levels.

4.5.1 Mortality

Four systematic reviews presented results regarding mortality in those referred early as opposed to late (Black et al. 2010, Chan et al. 2007, Kahn and Amedia 2008, Smart and Titus 2011). The primary studies common to more than one systematic review are highlighted in Table 4.3.

Table 4.3 Primary studies common to more than one systematic review investigating the impact of late referral upon mortality.

	Systematic Reviews – Kidney Disease: Mortality			
	Black et al. (2010)	Chan et al. (2007)	Kahn and Amedia (2008)	Smart and Titus (2011)
Primary Studies				
Avorn et al. (2002)	x			
Campbell et al. (1989)		x		
Cass et al. (2002)	x			x
Chesser and Baker (1999)		x		
Dogan et al. (2005)		x		
Ellis et al. (1998)	x	x		x
Fan et al. (2002)	x	x		
Frimat et al. (2004)			x	
Gallego et al. (2003)				x
Goncalves et al. (2004)		x		
Goransson et al. (2001)	x	x		
Hoffmann et al. (2006)				x
Iseki (2002)	x			
Jungers et al. (2001)	x	x		
Jungers et al. (2002)			x	
Jungers et al. (2006)				x
Kazmi et al. (2004)	x			
Kessler et al. (2003)			x	
Khan et al. (2005)	x		x	
Kinchen et al. (2002)	x	x	x	
Lhotta et al. (2003)	x	x	x	
Lin et al. (2003)	x	x		
Lin et al. (2004)	x		x	
Lorenzo et al. (2004)				x
Martinez-Ramirez et al. (2006)	x			
Orlando et al. (2007)	x			
Ratcliffe et al. (1984)		x		
Roderick et al. (2002a)		x		
Roderick et al. (2002b)		x		
Roubicek et al. (2000)	x	x	x	x
Sabath et al. (2003)			x	
Schmidt et al. (1998)		x	x	x
Schwenger et al. (2003)			x	
Schwenger et al. (2006)	x		x	
Sesso and Belasco (1996)	x			
Shin et al. (2007)	x			
Stack (2003)		x	x	x
Stoves et al. (2001)	x	x	x	x
Van Biesen et al. (1998)		x		
Winkelmayer et al. (2003)	x	x	x	x
Wu et al. (2003)	x			

As can be seen in Table 4.3 there is substantial overlap between the four systematic reviews. Roubicek et al. (2000), Stoves et al. (2001) and Winkelmayer (2003) appear in all four systematic reviews. Each of the four systematic reviews contains at least seven studies appearing in one of the other three reviews.

The results of the analyses pertaining to mortality in those referred early versus late are presented in Table 4.4 below.

All four systematic reviews found evidence to suggest that late referral resulted in significantly increased mortality as compared with patients referred early to nephrology care.

In their examination of the clinical effectiveness of early referral Black and colleagues found that in patients progressing to ESRD and surviving to dialysis, post-dialysis survival was improved by early referral. The differential effect of early referral to a specialist (> 72 months) on survival post-dialysis lasted for at least 5 years.

With regard to the impact of late referral upon mortality, Black and colleagues suggest that variability between studies may be explained by differences in baseline characteristics, the health care received and the small size of some of the studies. At 1 year, mortality was consistently higher in the late versus early referral group regardless of the definition of early referral. At longer follow-up, the majority of studies reported higher mortality in the late referral group. However, while absolute differences in mortality were observed, the relative difference, after adjusting for comorbidities, was less. We note that factors used for adjustment, which might be expected to influence results substantially, were variable: some studies employed socio-demographic characteristics and treatment regimens, with others limiting adjustment factors to age, sex and/or co-morbid conditions.

Chan and colleagues concluded that chronic kidney disease patients referred late to nephrologists have almost a two-fold risk of death as compared with earlier referred subjects and that the risk extended up to one year after the initiation of renal replacement therapy.

Kahn and Amedia (2008) found that the majority of evidence demonstrated worse survival with late referral. They attributed the results of a few studies showing no significant difference in long-term mortality to single-centre studies with small sample sizes.

The meta-analyses by Smart and Titus (2011) demonstrated that patients referred earlier to nephrology services had reduced mortality which was evident at three months and remained for 60 months (although lower mortality rates were most noticeable at 0-3 months). Interestingly, after three months, mortality rates between those referred early and late ran in parallel, which the authors suggested, may point to the fact that mortality difference between groups at later time points relates to the initial 0-3 month mortality.

Kidney Disease –Mortality

Table 4.4: Risk of death in early versus late referral

Review	Outcomes: Mortality	Outcomes: 5 years mortality	Outcomes: 1 year mortality	Outcomes: <1 year mortality
Black et al. (2010) *What is the evidence that early referral for CKD is clinically effective?*	In five retrospective studies constructed from cohorts starting on renal replacement therapy (RRT), mortality was reduced in the early referral group (more than 12 months prior to RRT) even as late as 5 years after initiation of RRT.	Adjusting for age, sex and comorbidities the RR of death for those with referral > 72 months prior to dialysis, as compared with< 6 months, was 0.53 (95% CI 0.35 to 0.79) at 5 years. (Jungers et al. 2001).	Adjusting for age, sex and comorbidities the RR of death for those with referral > 72 months prior to dialysis, as compared with< 6 months, was 0.24 (95% CI 0.10 to 0.59) at 1 year (Jungers et al. 2001). Lower 1-year mortality in those referred during the 24 months prior to dialysis (25–35%) as compared with those with no pre-dialysis referrals (51%)(HR 1.5 (95% CI 1.44 to 1.55) after adjustment for age, sex, ethnicity, treatment variation and comorbidities (Khan et al. 2005).	Adjusting for age, sex and comorbidities the RR of death for those with referral > 72 months prior to dialysis, as compared with< 6 months, was 0.13 (95% CI 0.03 to 0.58) at 3 months (Jungers et al. 2001).

Review	Outcomes: Mortality	Outcomes: 5 years mortality	Outcomes: 1 year mortality	Outcomes: <1 year mortality
Black et al. (2010) *What are the implications of late referral for CKD?*	Studies consistently reported higher mortality in the late referral group than in the early group at 1 year. The statistical significance of the differences was not reported in most studies.	No difference in risk of mortality at 5 yrs with referral timing after adjustment (HR 1.02, 95% CI 0.77 to 1.35) (Iseki et al. 2002) After adjustment, lower risk of death at 5 yrs in those referred early as compared to late: RR 0.45, 95% CI 0.25 to 0.81 (Lin et al. 2003). HR (haemodialysis) 0.45, 95% CI 0.25 to 0.81; HR (peritoneal dialysis) 0.29, 95% CI 0.07 to 0.48 (Lin et al. 2004). After adjustment, higher risk of death at 5 yrs in those referred early as compared to late: HR 1.19, 95% CI 1.05 to 1.35 (Cass et al. 2002) HR 1.43(0.115) p<0.001 (Stoves et al. 2008)	A statistically significant increase in risk of death at 1 year was found among those referred late (37–42% greater risk) after adjustment for confounders (Avorn et al. 2002, Kazmi et al. 2004). Non-significant difference (OR 1.03, 95% CI 0.84 to 1.25) between the groups at 1 year after adjustment for socio-demographics and comorbidities (Winkelymayer et al. 2003)	At six months, adjusted hazard ratio for late vs early referral HR 2.05 (95% CI 0.93 to 4.54) (Sesso and Belasco 1996).
Chan et al. (2007)	Late referral associated with significantly increased risk of death (RR 1.99; 95% CI, 1.66 to 2.39; p <0.0001).(20 studies, see Table 4.3, n=12,018)		At 1 year, relative risk (RR) of death of 2.08 in the late referred group (95% CI, 1.31 to 3.31, P=0.028). (? Studies, n=4777)	

Review	Outcomes: Mortality	Outcomes: 5 years mortality	Outcomes: 1 year mortality	Outcomes: <1 year mortality
Kahn and Amedia (2008)	Worse survival with late referral (11 studies: Frimat et al. 2004; Jungers 2002, Kessler et al. 2003, Khan et al. 2005, Kinchen et al. 2002, Lin et al. 2004, Schwenger et al. 2003, Schwenger et al. 2006, Stack 2003, Stoves et al. 2001, Winkelmayer et al. 2003. No significant differences in long-term mortality (3 studies: Roubicek et al. 2000, Schmidt et al. 1998, Lhotta et al. 2003). Cox proportional hazards regression analysis showed that those referred late had greater risk of death. While significant, association diminished after controlling for comorbidities, dialysis method and socio-demographic characteristics.			

Review	Outcomes: Mortality	Outcomes: 5 years mortality	Outcomes: 1 year mortality	Outcomes: <1 year mortality
Smart and Titus (2011)	Patients referred earlier showed a cumulative mortality benefit at 3, 6 and 12 months and 5 years compared with those referred late.	Patients referred early showed reduction in mortality at 5 years, pooled OR 0.45; 95% CI, 0.38-0.53; p<.00001) (3 studies: Jungers et al. 2006, Roubicek et al. 2000, Stoves et al. 2001)	Patients referred early showed reduction in mortality at 12 months, pooled OR 0.55; 95% CI, 0.50-0.60; p <.00001) (10 studies: Cass et al. 2002, Ellis et al. 1998, Gallego et al. 2003, Hoffman et al. 2006, Jungers et al. 2006, Lorenzo et al. 2004, Roubicek et al. 2000, Stack 2003, Stoves et al. 2000, Winkelmayer et al. 2003)	Patients referred early showed reduction in mortality at 6 months (1 study). Patients referred early showed reduction in mortality at 3 months (pooled OR 0.51: 95% CI, 0.44-0.59: p <.00001) (4 studies: Junger et al. 2006, Schmidt et al. 1998, Stoves et al. 2001, Winkelmayer et al. 2003)

4.5.2 Hospitalisation

Four systematic reviews presented results regarding hospitalisation in those referred early as opposed to late (Black et al. 2010, Chan et al. 2007, Kahn and Amedia 2008, Smart and Titus 2011). The primary studies common to more than one systematic review are highlighted in Table4.5.

Table 4.5: Primary studies common to more than one systematic review investigating the impact of late referral upon duration of hospitalisation.

Primary Studies	*Systematic Reviews – Kidney Disease: Hospitalisation*			
	Black et al. (2010)	Chan et al. (2007)	Kahn and Amedia (2008)	Smart and Titus (2011)
Dogan et al. (2005)		x	x	
Ellis et al. (1998)	x			
Frimat et al. (2004)			x	
Gallego et al. (2003)				x
Goransson and Bergrem (2001)	x		x	
Hoffmann et al. (2006)				x
Jungers et al. (2001)	x	x		
Jungers et al. (2002)			x	
Kessler et al. (2002)		x		
Ledoux et al. (2001)				x
Lhotta et al. (2003)	x	x		
Lorenzo et al. (2004)			x	
Orlando et al. (2007)	x			
Ravani et al. (2003)		x		
Riegel et al. (2005)			x	
Roderick et al. (2002a)	x			
Roderick et al. (2002b)		x		
Roubicek et al. (2000)	x	x	x	x
Sabath et al. (2003)			x	x
Van Biesen et al. (1998)		x		x

As can be seen in Table 4.5 there is substantial overlap between the four systematic reviews. Roubicek et al. (2000) appears in all four systematic reviews. Each of the four systematic reviews contains at least four studies appearing in one of the other three reviews.

The results of the analyses pertaining to hospitalisation in those referred early versus late are presented in Table 4.6 below.

All four systematic reviews found evidence to suggest that late referral resulted in a prolongation of initial hospital stay.

In their examination of the clinical effectiveness of early referral Black and colleagues found one study demonstrating little difference in hospitalisation days between those receiving specialist nephrology care and those receiving primary care only (Orlando et al. 2007). Two studies demonstrated shorter initial hospitalisation with earlier referral (Roderick et al. 2002a, Jungers et al. 2001).

With regard to the impact of late referral upon duration of initial hospitalisation, Black and colleagues found four studies all indicating that initial hospital stay was

longer in the patients referred late *vs* those referred earlier (Ellis et al. 1998, Lhotta et al. 2003, Roubicek et al. 2001, Goransson and Bergrem 2001).

The meta-analyses by Chan et al. (2007) and Smart and Titus (2011) found a reduction in the period of initial hospitalisation of 9 and 12 days respectively.

Table 4.6: Duration of initial hospitalisation in early versus late referral

Review	Outcomes: duration of hospitalisation
Black et al. (2010) *What is the evidence that early referral for CKD is clinically effective?* 3 studies	Group referred to nephrology specialists *vs* primary care only: mean 2.8 versus 2.5 days respectively; $p = 0.03$ (Orlando et al. 2007). Those referred < 1 month before dialysis had more hospitalisation episodes within first 6 months of dialysis than all others (1–4 months, 4–12 months and > 12 months) (mean 2.6 versus 1.7, $p = 0.001$). Median stay shorter when referred >1 month before dialysis (10 vs 18 days in < 1 month group) (Roderick et al. 2002a). Significantly shorter initial hospitalisation with referral ≥6 months before dialysis [mean 23.8 (SD 17.1) days] vs referred 6 - 35 months before dialysis [mean 7.5 (SD 8.9) days; $p <$ 0.001]. (Jungers et al. 2001).
Black et al. (2010) *What are the implications of late referral for CKD?* 4 studies	Median of 9.7 days hospitalisation in the early group and a median of 25 days in the late group (no *p*-value given) (Ellis et al. 1998). Mean initial hospital duration of 13 ±12.5 days for early referral patients and 19.5 ±14.1 days for late referral patients ($p = 0.04$). (Lhotta et al. 2003). Initial hospitalisation 20 ±21.5 days for the early referral group vs 33.3 ±21.8 days for late referral patients ($p < 0.001$) (Roubicek et al. 2001). Initial hospital stay more than four times longer for late vs early referral patients: median 31 (7–73) versus 7 (1–59) days *p* < 0.0001 (Goransson and Bergrem 2001).
Chan et al. (2007) 8 studies, n=3220	Pooled results from eight studies (see Table4.5) showed an initial hospital stay mean 25.3 ±3.8 days in late referred and 13.5 ±2.2 days in early referred patients. Prolonged duration of hospitalization in late referred group (average 12 days 95% CI, 8.0 to 16.1; p=0.0007).
Kahn and Amedia (2008)	Seven studies showed late referrals to nephrology had prolonged initial hospitalization (Dogan et al.2005, Goransson and Bergrem 2001, Jungers et al. 2002, Lorenzo et al. 2004, Riegel et al. 2005; Roubicek et al. 2000, Sabath et al. 2003). Type II diabetes patients starting dialysis in an emergency setting had significantly less nephrological care and significantly longer first hospital stay (Frimat et al. 2004).

Review	Outcomes: duration of hospitalisation
Smart and Titus (2011)	Pooled results from six studies (see Table4.5) showed shorter initial hospitalization in those referred earlier to a nephrologist: mean difference of -8.8 days (95% CI, -10.7 to -7.0 days p < 0.00001). Sub-analysis of those studies defining early referral between 3 and 4 months showed similar difference mean -7.7 days (95% CI -14.6 to -0.9 days; p = 0.03), and showed similar magnitude of reduction.

4.5.3 Peritoneal Dialysis

Rather than being filtered by an artificial membrane outside the body, peritoneal dialysis involves the blood being filtered through the thin membrane surrounding the organs in the abdomen. Peritoneal dialysis imposes fewer restrictions on diet and mobility.

Two of the reviews examined the uptake of peritoneal dialysis. Smart and Titus (2011) conducted a meta-analysis of 14 studies examining this outcome. Black et al. (2010) included data from two studies, one of which (Lin et al. 2004) was included in the Smart and Titus meta-analysis.

Taken together, the results of the two reviews indicate that peritoneal dialysis is more likely in patients referred early to nephrology care.

Smart and Titus (2011) found that peritoneal dialysis uptake was more common in those patients referred earlier to a nephrologist: OR 2.1 95% CI, 1.9 to 2.3; p <0.00001.

Black et al. (2010) noted that choice was available to both early and late referrals, although one of the two studies in their review (Fan et al. 2002) found that in the late referral group some participants were initiated on haemodialysis as an emergency.

4.5.4 Vascular Access

Permanent vascular access, which facilitates dialysis, is made possible with the preparation of a fistula (a direct connection between vein and artery, beneath the skin).

Two of the reviews examined permanent vascular access as an outcome in kidney disease patients referred early versus late: Black et al. (2010) and Smart and Titus (2001).

Only one of the studies (Goransson and Bergrem, 2001) appearing in Black et al. (2010) was also incorporated within the meta-analyses relating to permanent vascular access in the review by Smart and Titus (2011).

The results of both reviews suggested that permanent access was more likely, and temporary access less likely, in patients referred early to nephrology care.

Black et al. (2010) included three studies recording the percentage of haemodialysis patients with functioning permanent vascular access at the initiation

of dialysis. All three studies reported lower proportions of late referrals with permanent vascular access: 43% *vs* 0% (Goransson and Bergrem, 2001) 53.1% *vs* 0% (Sesso and Belasco, 1996) and 70.7% *vs* 26.9%, (Roubicek et al. 2000).

A meta-analysis within Smart and Titus (2010), pooling results from seven studies showed that permanent access, in terms of placement of arteriovenous fistulae, was more likely in earlier referred patients: OR 3.0, 95% CI, 2.5 to 3.5: p <0.00001.

Smart and Titus (2010) also conducted a further meta-analyses examining outcomes relating to *temporary* vascular access in early versus late referral. Pooled results from eleven studies recording the number of patients with temporary vascular access on initiation of dialysis, showed that patients referred earlier to a nephrologist were less likely to have temporary access at the start of dialysis: OR 0.18, 95% CI, 0.16 to 0.20; p< 0.00001.

4.5.5 Erythropoietin Use
Erythropoietin is a hormone secreted by the kidneys that controls the production of red blood cells. Anaemia may result if this process is disrupted.

Three systematic reviews presented results regarding use of erythropoietin in those referred early as opposed to late (Black et al. 2010; Kahn and Amedia, 2008; Smart and Titus, 2011).

One of the two studies appearing in the review conducted by Black and colleagues (Goransson and Bergrem, 2001), was also incorporated within a meta-analyses of seven studies relating to use of erythropoietin in Smart and Titus (2010).

Overall the pattern of evidence from the three reviews suggested that erythropoietin usage was more common in patients referred early to nephrology care.

Black et al. (2010) found evidence from two studies to suggest that pre-dialysis erythropoietin was prescribed more in those who were referred early (Goransson and Bergrem 2001, Lhotta et al. 2003).

Kahn and Amedia (2008) referenced a prospective community-based study of patients beginning kidney replacement therapy between 1997 and 1999 which found that early referral increased the likelihood of patients receiving erythropoeisis-stimulating proteins (ESP) (Thilly et al. 2006).

Smart and Titus conducted a meta-analysis of seven studies showing that erythropoietin usage was more common in patients referred early to nephrology care, OR 3.9, 95% CI 3.2 to 4.9 p<.00001) (Arora et al. 1999, Gallego et al. 2003, Goransson and Bergrem 2001, Hoffmann et al. 2006, Nakamura et al. 2007, Pena et al. 2006, Sabath et al. 2003, Stack 2003).

4.5.6 Serum Creatinine/ Creatinine Clearance

Creatinine is a waste product produced by muscles and excreted by the kidneys. Creatinine can be measured in the blood. High levels indicate that the kidneys are impaired. Creatinine levels can be used to assess the efficiency of dialysis.

Two systematic reviews presented results regarding serum creatinine and creatinine clearance in those referred early as opposed to late (Chan et al. 2007, Smart and Titus 2011). It was not possible to determine which primary studies contributed to the results presented for serum creatinine/creatinine clearance in the review by Chan and colleagues.

The results from both reviews suggest that serum creatinine levels are lower at dialysis initiation in patients referred earlier to nephrology services.

Chan et al. (2007) reported that mean serum creatinine and creatinine clearance were not significantly different between early and late referred groups: Serum creatinine (mg/dL) early 8.33 (0.32) late 8.96 (0.53) p = 0.103; Creatinine Clearance (mL/min) early 7.48 (0.69) late 6.51 (0.86) p = 0.47.

Smart and Titus (2011) conducted a meta-analysis of ten studies reporting serum creatinine levels which found lower levels at the start of dialysis in those patients referred to specialist care earlier, mean difference -93 µmol/L, (95% CI -112 to -73 µmol/L, p < 0.00001).

4.5.7 Haemoglobin

Anaemia may feature in kidney disease when there are not enough red blood cells, or not enough haemoglobin in the red blood cells to carry the usual amount of oxygen around the body.

Three systematic reviews presented results regarding haemoglobin levels in those referred early as opposed to late (Chan et al. 2007, Kahn and Amedia 2008, Smart and Titus 2011).

It was not possible to determine which primary studies contributed to the results presented for haemoglobin levels in the review by Chan and colleagues. The study included in Kahn and Amedia (2008) did not appear in the meta-analysis found in the Smart and Titus (2011) review.

Overall the pattern of evidence from the three reviews suggested that earlier referral was associated with higher haemoglobin levels.

Chan et al. (2007) found a trend toward higher haemoglobin values in the early referred group, which, did not reach statistical significance: Haemoglobin (g/dL) early 9.48 (0.36) late 9.05 (0.31) p = 0.07.

Smart and Titus (2011) conducted a meta-analysis of 12 studies reporting plasma haemoglobin levels, which showed higher levels (mean difference 11.1g.L-1 95% CI, 10.3-12g.L-1: P <0.00001) in patients referred to nephrology specialist services earlier.

Kahn and Amedia (2008) included the results from one study (Dogan et al. 2005) which found that late nephrologist referral was associated with lower serum haemoglobin at dialysis initiation.

4.6 Cost implications

Two systematic reviews presented results regarding the cost implications of delayed referral in chronic kidney disease (Black et al. 2010, Kahn and Amedia 2008).The results of both reviews suggest that earlier referral is associated with lower costs.

Black et al. (2010) included one Canadian economic evaluation of early versus late referral of patients with progressive renal insufficiency (McLaughlin et al. 2001). McLaughlin and colleagues developed a Markov model assessing the cost per life-year of nephrology referral for patients with late stage 4 CKD compared with nephrology referral upon development of uraemia. The analysis was conducted over a 5-year time horizon. The model predicted that earlier referral would increase survival and life-years free of dialysis, and reduce health service costs.

Black et al. (2010) also developed their own Markov cohort model to represent the natural history of CKD. Direct health service costs were then incorporated into the model. Alternative early referral strategies were then superimposed on top of the baseline model, and relative costs and consequences assessed. All early referral strategies produced more quality adjusted life-years (QALYs) than referral upon transit to stage 5 CKD. Referral for everyone with stage 3a CKD generated the most QALYs and, compared with referral for stage 4 CKD, had an incremental cost-effectiveness ratio of approximately £3806 per QALY.

Kahn and Amedia (2008) referenced the US renal data system 2006 annual data report (Collins et al. 2006) which showed that patients starting dialysis having previously seeing a nephrologist, and with adequate arteriovenous fistulae (vascular access – see section 4.5.4 above), consistently demonstrated the lowest annual costs.

4.7 Interventions

The included systematic reviews did not include any information regarding interventions to reduce delayed diagnosis or referral for CKD.

4.8 Types of Delay

None of the reviews estimated the average time intervals for any particular stage of the diagnostic process.

4.8.1 Patient delay
Patient non-compliance with appointments was identified as an important issue with an estimated 42% of late referrals attributed to this factor.

4.8.2 Doctor delay
Non-specialist and primary care physicians were less likely to refer patients early, less likely to refer non-symptomatic patients, less able to identify stage 3 and 4

CKD than specialists and one study found that over 90% of referring physicians judged that their training regarding timing or indication for referral for CKD was inadequate. A Canadian study found that physicians' decisions to refer were influenced by age, co-morbidities and distance to and overcrowding of dialysis centres. Lack of communication and faulty communication between primary care doctors and nephrologists were also identified as determinants of late referral.

4.8.3 System delay

The majority of studies suggested that late referral was more likely where patients were located in rural areas and further from specialist facilities. Conversely, one survey in three European regions found that late referral was more frequent in large city centres than regional centres. Physicians' decisions to refer were influenced by distance to and overcrowding of dialysis centres.

4.9 Discussion

Late referral to nephrology for kidney disease patients has a negative impact on several key outcomes, namely: mortality; length of hospital stay; uptake of optimal treatment; type of vascular access; levels of serum creatinine and haemoglobin; and finally, costs. However, for those patients with rapidly progressive kidney disease or chronic kidney disease which remains asymptomatic until a very advanced stage, late referral due to late presentation may be inevitable. Many of the primary studies within the included systematic reviews, and hence the systematic reviews themselves, did not distinguish between patients with and without the opportunity for timely evaluation by a specialist: in most cases late referral was defined simply as time before the initiation of dialysis or renal replacement therapy.

Recent research from the UK indicates that late referral to nephrology is a problem that the health service is beginning to tackle. Udayaraj et al. (2011) found that while late presentation with CKD was common (24.3%) among 894 adult patients attending one unit at an Oxford hospital, late referrals accounted for only 7.4% and 3.9% were avoidable. Furthermore, eleven centres (Basildon, Bradford, Dorset, Leeds, Middlesbrough, Nottingham, Oxford, Portsmouth, Sheffield, Stevenage and Wolverhampton), supplying data for approximately 11,000 patients between 2004 and 2009 show that the proportion of patients presenting less than three months before initiation of RRT had fallen from 27.1% in 2004 to 17.0% in 2009, possibly as a result of the publication of national clinical guidelines or the quality and outcomes framework initiative (UK Renal Registry 2010). Udayaraj et al. (2011) attributed a falling trend and lower incidence of late referrals at an Oxford hospital unit between 2003 and 2008 to implementation of automated estimated glomerular filtration rate reporting and increased awareness of CKD in primary care.

Nevertheless, recent research has identified an intervention which may further reduce the incidence of late referral. Farmer et al. (*in press*) assessed the impact of a computerised clinical decision support system (CDSS) to regularly screen patients having serum creatinine tests in primary care and found that 6% of the intervention group (n =98) were referred <90 days prior to commencing RRT as

opposed to 25% of those not exposed to CDSS (n=353). Furthermore, those patients referred late were subdivided into those where the requirement for RRT was predictable (sustained GFR<30 mL/min/1.73m^2 or rapidly declining renal function) and those not predictable. In this group 2% (n=2) of those exposed to CDSS were referred <90 days prior to commencing RRT as opposed to 15% (n=52) of those not exposed to CDSS (Farmer et al. *in press*).

With respect to the demographic determinants of delayed referral ,the findings of the UK Renal Registry Report (2010) were in accordance with our own, although they reported that patients who presented late were significantly older than patients who presented more than 90 days before dialysis initiation [median age 67.0 *vs* 64.7 years, p < 0.0001].

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5. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a long term condition, affecting mainly older people and smokers and involves a narrowing of the airways in the lungs. It is caused by harmful gases and particles, usually from smoking tobacco, which elicits an inflammatory response. It cannot be cured, and treatment aims to relieve symptoms and prevent exacerbations. Diagnosis confirmation requires use of a spirometer and is usually conducted in primary settings by trained staff.

5.1 Overall summary of findings

There is considerable under-diagnosis of COPD with most people with COPD being undiagnosed. Some regional variation has been identified; late diagnosis seems to be particularly marked in urban centres, particularly London.

Diagnostic rates seem to be affected by GP and nurse supply. Spirometry and reversibility testing were not uniform across all practices and areas, and staff reported a lack of confidence and training in the use of spirometers and interpretation of results.

Under diagnosis was associated with hospital admissions for exacerbations.

There was no information about the cost implications of delay in the included primary studies.

Strategies to improve diagnosis included case finding and using specialist services for respiratory assessment.

5.2 Included studies

No systematic reviews addressing late diagnosis and COPD were identified, but 12 primary studies examining this issue in the UK were found. One of these studies, Seamark et al. (2001), did not meet the minimum quality standard and so was excluded after quality appraisal. We present the findings from the remaining 11 studies.

Three studies conducted audits or tested the accuracy of diagnostic registers using spirometry (Bolton et al. 2004, Frank et al. 2006, Jones et al. 2008).

Four studies described and tested strategies to improve diagnosis, often case finding (Jordan et al. 2010, Tinkelman et al. 2006) or specialist services for respiratory assessment (Hassett et al. 2006, Walker et al. 2006).

Three studies analysed data from a large national survey, the Health Survey of England, to assess the prevalence of late diagnosis (Calderón-Larrañaga et al. 2010, Nacul et al. 2010, Shahab et al. 2006), and one study (Bastin et al. 2010) reviewed cases of patients admitted to hospital with an acute exacerbation of COPD, to find out how many already had a diagnosis.

Not all GP surgeries appear to have a spirometer and staff report a lack of training and / or confidence in operating one. Many studies, therefore, reported initiatives to improve the use of spirometers and to test the accuracy of COPD registers.

The characteristics of the studies examining late diagnosis of COPD are summarised in table 5.1.

Number of contributing studies: 11

Table 5.1: Characteristics of the studies

Study / Year [quality grade]	Research Design	Region	Participant characteristics	Disease state / condition
Bastin et al. 2010 [Medium]	Case Review	London	Sample size: 41 cases Patients admitted to hospital with acute exacerbation of COPD. All patients except one were smokers.	COPD was defined according to national guidelines, including the supporting information of a history of progressive breathlessness, and a chest radiograph consistent with COPD.
Bolton et al. 2004 [Medium]	Primary care staff survey about the use of spirometry. Case review of diagnosis in 2 general practices without spirometers.	Wales	Sample size: 227 responding practices, covering an estimated population of 1,415,647 (from 214 practices that reported) (approx. 49% of the population of Wales). 125 patients diagnosed with COPD. 62 Female 63 Male Mean age: 64.3 years (range 43-85); Never smoked: 6	Patients were studied when clinically stable, defined as no requirements for antibiotics or corticosteroids and no change in respiratory symptoms beyond normal day to day variation in the last month.

Study / Year [quality grade]	Research Design	Region	Participant characteristics	Disease state / condition
Calderón-Larrañaga et al. 2010 [High]	Secondary analysis of a national cross sectional study.	England	Sample size: 8064 GP practices. Mean average number of patients in GP practices: 6603 15-34 years: 27.5%; 35-74 years: 48.1%; 75+: 7.2% IMD score: 23.7 Smoking prevalence: 24.7%	The study uses the British Thoracic Society definition of COPD, that is, FEV1 divided by forced vital capacity (FVC) under 0.70, and FEV1 less than 80% of predicted.
Frank et al. 2006 [Medium]	Case finding	Greater Manchester	Sample: 825 patients Mean average age: 55.5 Female: 54.7%	The definition of COPD used in this study was based on spirometry results and was in accordance with the 2003 GOLD criteria. Subjects with GOLD stage 2-4 disease were classified as having COPD (FEV1< 80% predicted and FEV1/FVC ratio <70% after bronchodilation).
Hassett et al. 2006 [Medium]	Process evaluation	London	Sample: 16 GP practices, 330 patients with complete data. Age range 18 to 90 years (mean 62.97, SD 14.9) Male: 45% Smokers: 36% Ex-smokers : 41%	Not reported

Study / Year [quality grade]	Research Design	Region	Participant characteristics	Disease state / condition
Jones et al. 2008 [Medium]	Case Review	Devon, South West	Sample: 580 patients Mean average age: 68.1 Male: 64%	Spirometric results were interpreted according to the NICE recommendations. If reversibility testing was applied, diagnosis was based on post-bronchodilator values. A diagnosis of restriction was given if the FEV1 (% predicted) was <80% and the ratio of FEV1 to forced vital capacity (FVC) was ≥0.7.
Jordan et al. 2010 [High]	Secondary analysis and modelling.	England	Sample: 20 496 participants from the Health Survey of England. Hypothetical cohort of 10,000 patients for the modeling. Mean age was 51.8 years (SD 14.8) Female: 53% Current smokers: 25% Ex-smokers: 30.2%	Clinically significant COPD was defined as reporting of any respiratory symptom and evidence of airways obstruction on spirometry (forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <0.7 and FEV1 <80% predicted (equivalent to GOLD stage 2).
Nacul et al. 2010 [High]	Secondary analysis and modelling.	England	Sample size: 10,752 participants from the Health Survey of England with valid spirometry	COPD was defined using the British Thoracic Society (BTS) criteria: forced expiratory volume in 1s (FEV1) divided by forced vital capacity

Study / Year [quality grade]	Research Design	Region	Participant characteristics	Disease state / condition
			results.	(FVC) under 0.70, and FEV1 80% of predicted using reference values from the HSE. However in the HSE, spirometry was not carried out after bronchodilator challenge.
Shahab et al. 2006 [High]	Secondary analysis of the Health Survey of England data.	England	Sample size: 8215 patients with valid spirometric data. Mean (SD) age: 55.5 (13.5) Male: 46.4 % Manual occupation: 44.6% Mean (SD) deprivation score: 1.1 (1.2)	COPD is defined as an FEV1/FVC ratio below 0.7. In the presence of this obstruction, FEV1 above 80% of the predicted value is categorised as mild, FEV1 between 50% and 79% of the predicted value as moderate, FEV1 between 30% and 49% of the predicted value as severe, and FEV1 below 30% of the predicted value as very severe COPD. Since numbers in these latter two groups were small, they were combined for the purposes of this analysis.
Tinkelmann et al. 2006 [Medium]	Case Finding	Aberdeen, Scotland	Sample size: 401 patients Mean age 58.2 (SD ± 11.2) Male: 49.3%	A study diagnosis of COPD was defined as post-bronchodilator FEV1/FVC < 0.70. All study diagnoses were based on post bronchodilator spirometry values.

Study / Year [quality grade]	Research Design	Region	Participant characteristics	Disease state / condition
Walker et al. 2006 [Medium]	Case Review	Knowsley, North West	Sample size: 1508 underwent spirometry testing, 217 cases with complete data were reviewed. For 1508 patients: Mean age 57 years (SD ± 13) Female: 60% Current smokers: 50% Ex-smokers: 33% Never smokers: 17%	COPD defined as FEV1/FVC 0.7 and/or FEV1 80% predict ed.

5.3 Prevalence

Overall, the studies conclude that a large majority (approximately 80%) of cases of COPD are undiagnosed. Rates of diagnosis rise with increasing severity of COPD, but many cases of severe COPD remain undiagnosed. There is regional variation in rates of under-diagnosis, with London, Yorkshire and the north-east being singled out as having particularly poor diagnostic rates. Additionally, there is some doubt as to the accuracy of many GPs' COPD registers.

Studies which examine the prevalence of late diagnosis of COPD fall into three main areas: those based on data from the Health Survey of England; those examining the accuracy of COPD registers; and those conducting case analyses.

5.3.1 Analyses from the Health Survey of England
Shahab et al. (2006), Calderon-Larranaga et al. (2010), Nacul et al. (2010) and Jordan et al. (2010) used data from the Health Survey of England (HSE) to calculate the prevalence of late diagnosis for COPD. The HSE is a nationally representative, annual cross-sectional survey which, in 2001, focused on asthma and other respiratory problems. The survey consisted of a questionnaire and a home visit by a nurse, who conducted a spirometry test. Over 11,000 people had valid spirometry test results, and each study used these data in different ways. Jordan and colleagues used data from an earlier survey conducted in 1995-6.

Shahab and colleagues investigated the prevalence of COPD in HSE participants over 35 years old, with spirometry results and valid cotinine saliva samples (n=8,215). Nacul and colleagues used the HSE information to build a model, (incorporating practice level values of age, sex, ethnicity, deprivation, smoking and urbanisation), that would estimate under-diagnosis rates, and then investigated geographical patterns using classical and geographically weighted regression analysis. Calderon-Larranaga and colleagues examined associations between population characteristics, including diagnosed and undiagnosed prevalence (Nacul et al. 2007), primary healthcare factors, and COPD admission rates at PCT and practice levels in England. Lastly Jordan and colleagues used the data to model different types of case finding strategies, to see which would be most effective.

In 2001, the HSE survey found that 13.3% (95% CI 12.6 to 14.0) of the participants, aged 35 and over, had spirometry confirmed COPD (performed as part of the survey), but over 80% of these had had no previous respiratory disease diagnosis (Shahab et al. 2010). Shahab and colleagues reported that although the extent of under-diagnosis decreased significantly as the disease became more severe, even among those with severe or very severe COPD, only 46.8% (95% CI 39.1 to 54.6) had a diagnosis. In the mild stage, 6.4% had a diagnosis, and in the moderate stage, 21.3%.

Nacul and colleagues reported the expected prevalence of COPD in people over 15 years old in England to be 3.58%, or just over 1.4 million. The overall expected prevalence in all age groups was 2.58% (95% CI 2.49 to 2.66). The rate for 15–45 year olds was 1.32%, for 45–64s 4.22% and for those 65–74 and over 75 7.93 and 8.72%, respectively. Investigations into prevalence for each local authority revealed a range from 1.88 to 6.02%, with a median of 3.14% and an inter-quartile range (IQR) of 2.69-3.78%. The mean prevalence, taken from QOF diagnostic registers in local authority areas, was 1.37% (95% CI 1.33 to 1.42%), and varied between 0.65 and 3.13% (median: 1.29%, IQR: 1.05-1.61%). The ratio of diagnosed to expected prevalence in each local authority varied from 0.20 to 0.95, with a mean of 0.52 (95% CI 0.50 to 0.53).

There were some distinct geographical variations, with the North West and the North East regions having some of the highest prevalence observed, with the lowest prevalence of diagnosed cases in Southern England. The mean expected prevalence by region varied from 2.90% in the South East to 4.02% in the North East. For ratios of expected to observed COPD, there was significant variation (p< 0.001) between urban (mean ratio: 0.38, 95% CI 0.36 to 0.40) and rural areas (mean ratio: 0.56, 95% CI 0.54 to 0.58).The mean ratio of diagnosed to expected cases in London was lowest at 0.31 (95% CI 0.29 to 0.33). The study's analysis indicated that there are statistically significant clusters in the diagnosed: expected ratio for London and its hinterland, with the lower ratios found in London in sharp contrast to higher ratios found in areas surrounding the city. Similar clusters were found in other parts of England, particularly in Yorkshire and the North East; however these areas had higher diagnosed: expected ratios than London.

Calderon-Larranaga and colleagues were able to match all the data they required for their associations with 8064 GP practices from a total of 8932 (90.3%). They found that the mean overall average of registered COPD was 1.5% (SD 0.0%) and of undiagnosed COPD 2.2% (SD 0.1%), taking into account practice and PCT level analysis. They took the figure of a mean average of 3.8% of estimated prevalence from practice level predictions of COPD prevalence from the Association of Public Health Observatories to work out these prevalence figures. The mean ratio of observed to expected prevalence is 0.39.

Jordan and colleagues carried out a secondary analysis of the HSE, conducted in 1995-6. They found 971 participants had clinically significant COPD, and only 131 of these reported a diagnosis, suggesting that >85% were undiagnosed.

5.3.2 The accuracy of COPD registers in GP practices
Three studies conducted case reviews to test the accuracy of COPD registers in GP practices (Bolton et al. 2004, Jones et al. 2008, Walker et al. 2006), and Bastin et al. 2010 examined cases of hospital admission for acute exacerbation of COPD for records of a diagnosis.

Bolton et al. (2004) sent out questionnaires to all GP practices in Wales which asked about use of spirometry to confirm COPD diagnosis, and the confidence of staff to use the spirometer and interpret results. They did not ask about reversibility testing. They found that spirometric confirmation of COPD ranged from 0% to 100%, with a median of 37% in the 87 respondents giving this information. In practices that were confident in the use of a spirometer, the percentage of patients with COPD confirmed this way, was median 50.5%, (n=50, p=0.155) and for those confident with interpretation, the median was 54.7%, (n=34, p=0.022) compared with those with less confidence (confirmation median 29.4%,(n=25) and interpretation median 30.7%, (n=39)). The researchers also carried out spirometry testing on 125 patients who had a diagnosis of COPD from two practices in Cardiff, which had been made on the basis of personal history and examination, but not spirometry. Of these, 61 (48.8%) had confirmation of COPD, 25 (20%) had reversible obstruction (range 210-800mls), 34(27.7%) had normal spirograms (4 of the 6 non-smokers) and 5(4%) had restrictive spirometry.

Jones et al. (2008) audited 16 GP practices in Plymouth and North Devon over a year, by carrying out spirometry and reversibility testing on patients from the COPD registers. Of the 580 patients completing spirometry, 158 (27%) did not have COPD, according to NICE guidelines, and of the 422 patients who had a confirmation of COPD, 25 (6%) had both asthma and COPD. Reversibility testing was carried out on 232 (51%) patients and the severity rating of the disease based on pre-bronchodilator readings changed after bronchodilaton in 41(18%) patients, with 31 moving from a moderate to a mild rating, and 10 from severe to moderate. The authors concluded that the diagnostic registers in primary care in the area were inaccurate in 27% of cases. Reversibility testing showed that pre-bronchodilator readings alone overestimated both the prevalence and the severity of COPD.

Walker et al. (2006) assessed the impact on diagnosis, over the period 1999 to 2003, of an open access service for spirometry for practices in Knowsley. GPs were

encouraged to refer patients with respiratory symptoms to the service for diagnosis confirmation. The total number of patients referred and attended was 1,508, and of these, 469 patients underwent reversibility testing as well as spirometry. They examined the medical notes of 217 patients from 5 randomly selected practices, out of a total of 11 referring practices. Of the 139 patients diagnosed with COPD, 48 (34.5%) had a previous diagnosis, 31 (22.3%) had been misdiagnosed with asthma, and 60 (43.2%) had been previously undiagnosed. After reversibility testing, 76/469 patients had no airflow obstruction.

5.3.3 Case analyses

Bastin et al. (2010) reviewed cases of first admissions with an acute exacerbation of COPD over a period of a year (2005/6) to a north London hospital. They identified 41 patients of which 14 (34%) had not been previously diagnosed with COPD. These patients had COPD that was as severe and symptomatic as previously diagnosed patients; three (21%) patients with respiratory acidosis at admission, and seven (54%) patients with MRC dyspnoea scale breathlessness of grade 3 or more. Age, spirometry results and hospital length of stay were not significantly different from patients who had COPD diagnosed prior to hospital admission.

Two studies pursued case finding to assess the prevalence of undiagnosed COPD (Tinkelmann et al. 2006, Frank et al. 2006).

Tinkelmann and colleagues and Frank and colleagues invited patients for spirometry, the sample information, strategy and results are presented in table 5.2.

The prevalence of undiagnosed COPD varied from 63.2% (103/163 patients) (Frank et al. 2006) and 22% (88/401 patients) (Tinkelmann et al. 2006). The degree of severity of undiagnosed patients is shown in table 5.3.

Frank and colleagues noted that almost half (46%) of the individuals with confirmed COPD (GOLD stage 2-4) had no record of prescribed inhaled medication in the previous year. Some patients were over diagnosed. In 28 out of 88 patients (31.8%) who had practice-recorded diagnoses of COPD, the spirometry results did not support this diagnosis (GOLD stage 2-4) although 14 of these patients would be classified as having GOLD stage 0 (at risk but with normal spirometry) or GOLD stage 1 (FEV1 ≥80% predicted and FEV1/FVC<70%).

Table 5.2: Sample information for case finding studies.

Study	No. of participating practices	No. of patients attending for testing	Inclusion criteria	Exclusion criteria	No. completing tests
Frank et al. 2006	2	871	Aged 30 or more, smoker, reported respiratory symptoms	-	825
Tinkelmann et al. 2006	-	-	Aged 40 or older Current or former smoker	No prior diagnosis of any chronic obstructive respiratory disease; history of known pre-existing or concomitant non-obstructive lung disease; acute symptoms suggestive of unstable heart disease.	401

Table 5.3: Degree of severity (GOLD criteria) for those without a diagnosis (no. of patients)

Study	At risk	Mild	Moderate	Severe	Very severe
Frank et al. 2006	57	13	69	10	1
Tinkelman et al. 2006	-	47	34	7	-

5.4 Determinants

Three studies contained information about the determinants of diagnostic delay (Bolton et al. 2004, Jordan et al. 2010, Nacul et al. 2010). People with COPD who have never smoked are less likely to be diagnosed than those with a history of smoking and the prevalence of undiagnosed clinically significant COPD increases with age. The supply of GPs is associated with diagnostic rates though this is not the only system factor associated with late diagnosis. The availability of a

spirometer and the competence of staff – both in use and interpretation of results – is also a factor.

5.4.1 Demographic

Jordan and colleagues described the characteristics of participants with undiagnosed COPD. There was a greater proportion of females among undiagnosed cases, however, this was not significant (41.7% *vs* 35.9%, p=0.2). Undiagnosed cases were more likely to be never smokers (16.8% *vs* 6.9%, p=0.002). Prevalence of undiagnosed clinically significant COPD increased with age, from 0.2% (30 - 39 yrs group), to 12.9% ≤80 yrs group). This was highest among smokers for all ages, rising from the age of 40-45 years. Among ex-smokers, undiagnosed prevalence remained at or below 1% until 55 years, and for never smokers the rate did not go beyond 1% until 60 years.

5.4.2 Medical

5.4.2.1 Disease Severity

Jordan and colleagues reported that undiagnosed patients were less likely to report any specific respiratory symptoms and their dyspnoea grade was lower (38.5% had MRC grade 3 dyspnoea *vs*. 69.5% with a diagnosis). Airways obstruction was milder in undiagnosed cases (p<0.001), however a quarter had severe airways obstruction (FEV_1<50%) and thus would be eligible for inhaled medication.

5.4.3 System

When Nacul and colleagues added GP supply as an independent variable to their model, they found it increased the local correlation coefficient for most local authorities, particularly for the East Midlands. This suggests that the supply of primary care affects diagnostic rates.

Bolton and colleagues examined the use of spirometry in GP practices in Wales, to find out the extent of use, confidence in use and interpretation, and the amount of training staff had been given to use the equipment. They sent a questionnaire to surgeries and 227 responded.

Not every practice had a spirometer and even if they had one, not all used it: 187 (82.4%) practices had a spirometer and of these 160 (85.6%) used it. Of the 160 practices which reported using a spirometer, 21.9% used it for diagnosis in every suspected case, with 33.8% using it often, and 44.4% using it sometimes or rarely. Usually the practice nurse carried out the test, with 34 practices reporting both the doctor and nurse completing the test.

Practitioners were not necessarily confident about the use of a spirometer or the interpretation of results. Greater confidence was seen in staff that used the spirometer in every case of suspected COPD, 28 of the 35 (80%) practices who reported this. This percentage reduced to 74% with practices who reported that they used the spirometer often. Spirometry was performed more often in practices confident in use (p<0.001). Fewer practices reported satisfaction with interpretation of results – only 54 (33.8%) – while 104 practices reported limited or no confidence. Again, spirometry was performed more often in those who were

confident in interpreting the results, compared with those who were less confident (p<0.001). For example, in those practices where every suspected case of COPD was diagnosed using spirometry, 62% were confident with their interpretation.

Lack of training in the use of spirometry contributed to the lack of confidence in using the equipment. In those practices reporting use and confidence, the median amount of time spent on training was 6 hours (range 0-20h). In those practices not confident in the use of the spirometer it was only 1hour (range 0-14h) (p<0.001). For practices with a spirometer but not using it (8/11 responses), median training time was 30 minutes (range 0-4h).

Similarly training in interpretation of results impacted on feelings of confidence in this area. Thirteen practices reported no training. Those confident with interpretation reported a median average of 4 hours (range 1-15h), those with limited confidence, a median of 2 hours (range 0-30h), those not confident, a median of 0.6 hours (range 0-3h) (p<0.001). For those who possessed a spirometer but did not use it (6/11 responses) the median average time in training was 0 hours (range 0-2.5 h).

Forty practices did not have a spirometer, and of these three had open access to hospital lung function, 31 did not and six gave no answer. Only one practice reported using hospital lung function in every case of COPD and two used it sometimes.

5.5 Outcomes

Only one study (Calderon Larrenaga et al. 2010) looked at the impacts of undiagnosed prevalence on, specifically, hospital admissions.

When Calderon-Larrenaga and colleagues investigated hospital admissions during the financial years of 2006/7, 2007/8 and 2008/9, they were able to show a strong association between undiagnosed prevalence and hospital admission at a practice level, (incidence rate ratio: 1.045, 95% CI 1.032 to 1.059, p<0.001) through Poisson regression analysis. Undiagnosed prevalence was a risk factor alongside registered prevalence, deprivation and smoking prevalence. Primary healthcare factors such as being offered influenza immunization, access to GPs within 2 days and primary care supply were protective factors (p<0.05).

5.6 Cost Implications

There was no information about the cost implications of late diagnosis for COPD.

5.7 Interventions

Since much of the delay in diagnosis appears to rest on the use of spirometry in primary care practices, interventions focused on case finding and improving spirometry use in GP practices. Some interventions, such as auditing to improve the accuracy of registers have been described in the prevalence section above. One study (Walker et al. 2006) described the impact that spirometry had on subsequent medication, which is reported here, although some of the patients may have been diagnosed before spirometry confirmation.

Three studies reported on interventions to improve the diagnosis of COPD (Hassett et al. 2006, Jordan et al. 2010, and Walker et al. 2006). Strategies to improve diagnosis included case finding and using specialist services for respiratory assessment.

Jordan and colleagues modelled two case finding strategies to find which was the most effective in identifying new cases of COPD. Patients at risk of COPD (ever smokers aged 40–79 years) would be identified from general practice records and targeted in two ways:

1. The opportunistic approach would use patient records to flag the need for doctors and nurses to ask simple questions about respiratory symptoms during consultations.
2. The active case finding approach would add a postal questionnaire with the same respiratory questions to the opportunistic approach.

Patients with positive respiratory symptoms (defined according to the NICE criteria) would be invited for spirometry and then classified as having COPD or not.

Their analysis of the HSE, (n=20,496), showed that 48% of the target group reported relevant symptoms. Of these, 16% demonstrated airways obstruction, and therefore, for every 10,000 ever-smoking patients in this age group, 768 undiagnosed cases (or 7.7 per 100) would be expected. The active approach to case finding would yield 70% more new cases than the opportunistic approach (3.8 *vs* 2.2 new cases per 100 ever smokers targeted), giving a rate difference of 1.6 per 100 targeted and identifying 49% of the expected cases. Sixty-three ever smokers would need to be actively targeted to identify one extra case of COPD, over and above the opportunistic approach. Of these new cases, 39.2% would have at least MRC grade 3 dyspnoea, and 26.8% stage III/IV disease (50.9% with either) (figures from the HSE analysis) and could benefit immediately from effective disease-modifying treatments.

They conducted a sensitivity analysis on key parameters and found that the modifiable parameters are the response rate to postal questionnaires, the probability that the questionnaire is administered opportunistically and the spirometry uptake rates. A variation in postal response of 30–70% would result in a rate difference of 1.0–2.2 per 100 targeted. In contrast, as practices administer more questionnaires, the advantage of the active approach is attenuated.

They modelled alternative targeting strategies. Targeting those aged over 50 increases the efficiency of an active approach compared with an opportunistic-only approach (NNT 47 *vs* 65) although marginally less sensitive than targeting the full 40 - 79 year age range (44% *vs* 49% of the expected cases). Targeting current smokers aged ≥45 years and ex-smokers aged ≥55 years would improve the efficiency of the active approach without losing many cases (NNT=45; 47% total identified). A strategy that just used a postal questionnaire would result in a difference of only 0.5 per 100 targeted over the base case, and identify one third fewer cases than with the combined approach.

Restricting the target group to those with dyspnoea only would identify patients with more severe disease (50.4% with MRC grade 3 dyspnoea *vs* 39.2% in the base case), but the active approach would then have a relatively smaller benefit and pick up fewer undiagnosed cases than the base case. Use of the single LLN (lower limit of normal) criteria to define cases had little overall effect, although cases were generally milder. While double LLN decreased the yield in both arms, and reduced the advantage of the active approach, a higher proportion of more severe cases would be identified (59.0% eligible for disease-modifying treatment).

Hassett and colleagues described a process evaluation of a Community Respiratory Assessment Unit (CRAU) set up and run by the PCT in Hammersmith and Fulham. It was staffed by 2 nurses specialising in respiratory diseases who conducted diagnosis with spirometry, gave feedback to GPs, and supported GP education with leaflets to be used with patients, including information on smoking cessation. Initially, it was based in Charing Cross Hospital but latterly a peripatetic service was added for practices at the northernmost and southernmost parts of the PCT, farthest away from the hospital. While definite or suspected COPD was the most common reason for referral (189/330 - 57% of all referrals), airway narrowing was only demonstrated in 110 of those 189 cases (58%). Eight of those patients had significant reversibility, suggesting at least a significant component of asthma. A quarter of patients referred with definite or suspected COPD had no abnormalities at all detected during the assessment. Nineteen (17%) had an unexpected restrictive / small lung disorder and 53% of those (10/19) had a BMI greater than 30.

Walker and colleagues described changes to therapy for COPD patients within 3 months of spirometry testing. Of the 132 patients identified, 85 were current smokers, and 65 (76%) were given smoking cessation advice in the follow up to their diagnosis. Spirometry testing led to increases in prescriptions of short and long acting bronchodilators and inhaled corticosteroids. Prescription of short-acting ß-agonists increased from 79 to 97% (p = NS) of patients, short- and long-acting anticholinergics from 18 to 37% (p=0.003) and long-acting ß-agonists from 8 to 25% (p<0.001). In total, 22 COPD patients (17%) were referred to secondary care within 6 months of spirometry testing. Further pharmaceutical additions to currently prescribed treatment were made In six out of these 22 subjects, the referral specifically requested pulmonary rehabilitation. Before spirometry testing, four subjects had completed pulmonary rehabilitation and after testing a further 10 subjects were referred and completed the course (p=0.018).

5.8 Types of delay

Confirmation of diagnosis seems to be delayed because of the lack of confidence in the use of spirometry. COPD is more prevalent in smokers and ex-smokers over the age of 45 and this fact has aided researchers in improving diagnosis through case finding and auditing strategies.

5.8.1 System Delay
Two studies (Calderon Larrenaga et al. 2010, Nacul et al. 2010) used modelling to show that the supply of GPs affects the rate of diagnosis. There were marked

discrepancies in the expected: observed ratio for the diagnosis of COPD between urban and rural areas, with London, for example, having a lower ratio of expected to observed cases than its hinterland.

Lack of training in spirometry, leading to lack of confidence for staff in primary care sites, in turn led to equipment not being routinely used. Without an accurate diagnosis, based on spirometry and reversibility testing, patients have had a diagnosis of asthma, or a diagnosis of a more severe stage of COPD, no diagnosis at all, or a diagnosis of COPD when they have normal spirograms. These diagnostic outcomes have had consequences in the type of medication and management that patients received, and increased the likelihood of exacerbation.

5.9 Discussion

COPD has a particularly high prevalence of late diagnosis, with an estimated 80% of cases remaining undiagnosed. Under-diagnosis was associated with costly hospital admissions for exacerbations of the condition. Avoiding crises is important for the patient as frequent exacerbations result in significantly faster decline (Donaldson et al. 2002) and a greater risk of mortality (Soler-Cataluna et al. 2005).

Unfortunately, while evidence suggested that there was a strong association between undiagnosed prevalence and hospital admission at a practice level, information regarding the outcomes of delayed diagnosis was otherwise lacking from this review. Nevertheless, it has been reported elsewhere that exacerbations (with attendant hospitalisation and risk of death) are common even for those with moderate stages of the disease (Hurst et al. 2010).

It is notable, therefore, that airways obstruction was milder in undiagnosed cases as recent studies have shown that lung function declines faster in the earlier stages of the disease (Jenkins et al. 2009, Decramer et al. 2009). Exacerbations, leading to hospitalisation, may also be avoided if patients with the condition are recognised and treated earlier (Celli et al. 2008, Seemungal et al. 1998), although Seemungal and colleagues found that 50% of exacerbations were unreported. Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009).

It would appear that enhancing the appropriate use of spirometers in primary care presents an opportunity to reduce delays to the diagnosis and prompt treatment of COPD. Lack of training in spirometry, leading to lack of confidence for staff in primary care sites, in turn led to equipment not being routinely used. Without an accurate diagnosis, based on spirometry and reversibility testing, patients were diagnosed with asthma, a more severe stage of COPD, had no diagnosis at all, or a diagnosis of COPD when they had normal spirograms. These diagnostic outcomes have had consequences in the type of medication and management that patients received, and increased the likelihood of exacerbation

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6. Dementia

Dementia is a long term condition and early detection has consequences for patients, families, and the health care system. The included reviews focus on the barriers to diagnosis, highlighting therapeutic nihilism and the apparent dearth of supportive services for people with this condition.

6.1 Overall summary of findings

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases.

Fear of a diagnosis affected patients and families, and made them reluctant to seek help. Fears centred round stigma, loss of independence and beliefs that nothing could be done. Primary care physicians shared the therapeutic nihilism of their patients and worried that a diagnosis would bring expectations of care that they could not fulfil.

Doctors acknowledged their difficulties in recognising the early stages of dementia and conducting tests in the short time available in a typical surgery consultation.

There was no information regarding either the outcomes or cost implications of late diagnosis of dementia in the included reviews.

Educational interventions increased healthcare practitioners' knowledge of dementia. Specifically, decision support software, practice based workshops and in- home assessment by nurses increased detection rates.

6.2 Included Studies

We found three systematic reviews examining late diagnosis and dementia (Bradford et al. 2009, Koch et al. 2010, Koch and Iliffe 2011).

Bradford et al. (2009) conducted a systematic review to gauge the prevalence of the condition and to describe the contributing factors for missed and delayed dementia diagnoses in primary care.

Koch et al. (2010) investigated barriers to the early detection of dementia. Koch and Iliffe (2011) identified interventions that aimed to improve the early diagnosis of dementia and also examined the management of dementia. With regard to the latter study we present material here from the studies which concern diagnosis only (n=5).

The characteristics of the included reviews examining late diagnosis in dementia are presented in Table 6.1.

Number of contributing reviews: 3

Table 6.1: Characteristics of reviews examining delayed diagnosis of dementia.

Systematic review [AMSTAR score]	No. included studies	Pooled number of participants	Countries	Participants	Disease State/ Condition
Bradford et al. 2009 [8/11]	40 studies 8 = rate of missed diagnosis; 32 = risk factors for missed diagnosis	2160	Not reported	In the 8 diagnostic accuracy studies: patients >64 yrs old Providers: primary care physicians	Not reported
Koch et al. 2010 [7/11]	11 studies	>1300	Not reported	Health care professionals, primary care physicians, patients or carers	Not reported
Koch and Illife 2011 [10/11]*	5 studies relevant to diagnosis of dementia	1,652 GPs; 35 GP practices; 3172 patients; 214 specialists	Denmark France Germany Holland UK	GPs, specialists, dementia patients and caregivers	Not reported
Those studies marked with an asterix satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool (see Appendix 2).					

Seven primary studies were common to both Bradford et al. (2009) and Koch et al. (2010). Full details of the overlap of studies between these two reviews can be found in Table A5.1 in Appendix 5.

6.3 Prevalence

Bradford et al. (2009) found that diagnostic accuracy was poorest among patients with few or mild symptoms of dementia. Primary care providers' diagnostic sensitivity ranged from 0.09 to 0.41 in the milder stages, in contrast to a diagnostic sensitivity range of 0.60 to 1.0 in severe cases. The overall sensitivity of providers' diagnoses relative to standardized assessments varied widely among studies, ranging from 0.26 to 0.69.

Although Bradford and colleagues estimated the pooled sensitivity across studies as 0.49 (384 true positives out of 791 cases, collapsed across severity categories), they warned that the studies were methodologically heterogeneous, and the estimate did not take account of nesting within studies. There was considerable variability in sensitivity estimates even when groups of studies used similar diagnostic methods, for example DSM criteria as the reference criteria produced

estimates of diagnostic sensitivity that ranged from 0.29 (Olafsdottir et al. 2000) to 0.60 (Verhey et al. 1993).

6.4 Determinants

There was considerable overlap between Bradford et al. (2009) and Koch et al. (2010). Factors associated with late diagnosis of dementia are described in Table 6.2, with the number of primary papers contributing to each, and whether the determinant was recorded as a barrier (+) or a facilitator (-) to diagnosis.

Table 6.2: Determinants of late diagnosis for dementia

Determinant	Bradford et al. (2009) (no. of contributing primary studies)	Koch et al. (2010) (no. of contributing primary studies)
Demographic	**Gender** Female (1+) **Age** Older age (1+, 1-) Caregivers: Younger age (1+) **Socio-economic status** Lower education level (1+) Caregivers: Lower level of education (1+) **Place of residence** Rural residence (1+) Caregivers: Rural residence (1+) **Marital status** Single (1+)	
Medical	**Co-morbidities (2+)** Presence of depression (2+) **Disease Severity (8+)** More difficult to diagnose in the milder stages **Other** Patient impairment (4+); Type of Dementia (2+) Alzheimer's dementia more readily detected; Associations between detection of dementia and the degree of impairment or dependence on a caregiver	**Co-morbidities (3+)** **Non-specific presentation (3+)** Particularly in the early stages

Determinant	Bradford et al. (2009) (no. of contributing primary studies)	Koch et al. (2010) (no. of contributing primary studies)
System	**Access** Frequency of contact with PCP (2-); Geographical and transportation barriers (2+); Lack of provider availability (3+); Financial barriers (4+) **Resource Constraints** Lack of time for PCP to assess patients in a typical visit (7+); Lack of services for dementia patients (7+); Lack of availability of specialists during diagnosis (3+); Low financial reimbursement for dementia care (2+); Restricted access to dementia care by health payers (2+); Lack of assessment tools and protocols (2+) or lack of tools perceived as helpful (3+); Limitations on diagnostic tools (2+) **Health system restrictions** Dementia not prioritized in planning (3+).	**Resource Constraints** Insufficient support to meet expectations (1+); Lack of time for PCP to assess patients in a typical visit (5+); Limited access to secondary services (2+); Low financial reimbursement for dementia care (5+)
Knowledge, attitudes and beliefs of patients and caregivers	Stigma (7+) Dementia diagnosis would be impediment to accessing residential care or other services (1+) Patient refusal to be assessed or treated if diagnosed (8+) Distress about the possibility of dementia (1+) Low prioritization of cognitive function concerns (1+) Patients and /or family in denial about deterioration (9+).	Stigma (1+) Mental illness, loss of independence, nursing home needs (1+) Patients and /or family in denial about deterioration (1+). Families compensating for the patient so they don't notice the illness (1+) Lack of knowledge, attributing symptoms to 'normal ageing' (2+)

Determinant	Bradford et al. (2009) (no. of contributing primary studies)	Koch et al. (2010) (no. of contributing primary studies)
	Lack of knowledge, attributing symptoms to 'normal ageing' (8+) Lack of knowledge, misattribution of symptoms (6+) The perception of limited treatment options (4+). Immigrants concern that seeking dementia care would lead to deportation or change in immigration status (1+). Diagnosis viewed as too time consuming by caregivers (2+) Caregiver: fear of confirming own risk of dementia (1+) Emotional, financial and other burden of diagnosis on the caregiver or family (4+) Concern about the effects of diagnosis on the patient's autonomy (2+), or involvement of social services (1+)	
Knowledge, attitudes and beliefs of doctors	Older age: older doctors more confident about making a diagnosis, younger doctors were more knowledgeable (1) Lack of knowledge about dementia care (16+) Lack of knowledge about what constitutes 'normal ageing' (3+) Perceived difficulty of detecting and / or managing dementia (8+) Concern about the consequences of misdiagnosing dementia (5+) Stigmatizing effects of diagnosis (7+)	Female and more experienced primary care physicians (PCP) more pessimistic "heartsink attitudes"(1+) Stigmatizing effects of diagnosis Assumed that patients did not want a diagnosis (1+) Fear of giving the wrong diagnosis leading to legal action (1+) or damaged relationship with patient (2+) Therapeutic nihilism (2+) PCPs believe that early diagnosis is undesirable (1+) because there is no adequate treatment or benefits to making a diagnosis.

Determinant	Bradford et al. (2009) (no. of contributing primary studies)	Koch et al. (2010) (no. of contributing primary studies)
	Therapeutic nihilism PCPs believe that early diagnosis is undesirable (8+) because there is no adequate treatment or benefits to making a diagnosis (6+). Unwillingness to discuss cognitive function with patients and carers (1+). Low prioritization of cognitive problems relative to physical health problems (1+). Avoidance of pressure for intervention once diagnosis is made (1+), which would strain the resources of their practices (4+). Discomfort at administering assessment instruments or procedures (1+). Reluctance to seek speciality consultation or referrals (1+) Perception that specialists should make the diagnosis (2+)	Lack of satisfaction with specialist input (2+) Inadequate training leading to lack of confidence about making a diagnosis (4+) Only a minority used validated instruments to diagnose dementia (1+) Perception that early detection was the most difficult part of the illness (1+)
Communication barriers	Communication Problems (7+); Difficulty disclosing diagnosis (5+); Language barriers (1+); Poor communication skills (1+); Patients relying on PCP to broach the topic of cognitive function (1+); Patients declining to challenge the PCP's authority (1+); Perceptions of disparities or discrimination in care (1+)	Lack of knowledge about how to disclose the diagnosis (1+); PCPs informed families but not the patients (1+)

Determinants: Key Findings

Demographic

- Caregiver age, gender, ethnicity, socio-economic status (low level s of education),rural residence and marital status were associated with delays in diagnosis.

Medical

- Co-morbidities, particularly depression, were found to predict delays.
- Early detection was hampered by non-specific presentation and fluctuating symptoms.
- Patient impairment was associated with delays.
- Alzheimer's disease was more readily detected than other forms of dementia.

System

- Patients experienced barriers to accessing services, specifically transportation, geographical and financial. It was found that frequency of contact with PCPs increased the likelihood of timely diagnosis.
- PCPs complained that there was a lack of time in a typical surgery visit to fully assess and diagnose the patient.
- PCPs thought there was a lack of services available for the care of patients with dementia, and the rates of financial reimbursement for dementia care were low.
- There was limited access to specialist support during diagnosis and restrictions on diagnostic tools.
- There were few assessment tools and protocols, and some were not considered helpful.

Patients' and caregivers' knowledge, beliefs and attitudes

- A diagnosis of dementia carried some stigma associated with a mental illness diagnosis and fears about loss of independence and needing nursing home care. Distress about the possibility of dementia was reported and some patients refused to be assessed or treated, if diagnosed.
- Families were in denial about deterioration in cognitive performance, or were so used to compensating for their relative's reduced functioning that they did not notice changes. There was a low priority given by families to cognitive functioning concerns.
- Families misattributed symptoms to signs of normal ageing and there was a lack of knowledge about the condition.
- Patients and families believed that there were limited treatment options.

Primary Care Physicians' knowledge, beliefs and attitudes

- PCPs considered that they had insufficient knowledge, and / or lack of confidence in their ability, to make a diagnosis of dementia. An absence of specific training at medical school or continuing professional educational courses to support diagnosis was identified. Early detection was considered particularly difficult.
- PCPs expressed anxiety about misdiagnosis and the harm it might do to their relationship with their patients.
- PCPs thought that early diagnosis was undesirable since there were few treatment options, and a diagnosis of dementia could have a stigmatizing effect on patients.
- They were also concerned that they could not provide the care that was expected, and avoiding a diagnosis lessened the pressures on services. There was a lack of knowledge about the support services available, generally.
- PCPs were unwilling to discuss with patients cognitive functioning, and gave it lower priority than physical functioning.
- They expressed discomfort in administering the cognitive tests necessary for diagnosis, but were also reluctant to refer patients for specialist help. However, there was a perception that specialists should make the diagnosis.

Communication Barriers

- For PCPs, there were difficulties in disclosing and explaining the diagnosis. Sometimes there were language barriers. Some PCPs lacked communication skills.
- Patients relied on the doctor to bring up the issue of cognitive functioning, rather than initiating the discussion themselves. They also declined to challenge the authority of the doctor.

6.5 Outcomes

None of the included reviews presented data relating to the outcomes of late diagnosis for dementia.

6.6 Cost implications

None of the included reviews presented data relating to the cost implications of late diagnosis for dementia.

6.7 Interventions

There was one systematic review, Koch and Iliffe (2011), which brought together evidence from trials of interventions aiming to improve the detection and management of dementia. There were 5 trials that focused solely or partly on diagnosis (Downs et al. 2006, Rondeau et al. 2008, Vollmer et al. 2010, Perry et al. 2008, Waldorff et al. 2003).

All of the interventions were directed at health professionals in primary care: doctors and / or nurses.

Downs and colleagues (2006) described a cluster randomised control study that trialled three interventions:

- Decision support software, connected to electronic records, and using prompts for the investigation of dementia
- Self-directed learning with a tutorial on CD-ROM
- Practice-based workshops, facilitated by GPs, using clinical scenarios and case discussions in multi-disciplinary groups.

The study was able to show that the software and the workshop significantly increased the detection of dementia by 30% (p=0.01) and 31% (p=0.02) respectively.

Rondeau and colleagues (2008) examined whether educational seminars or workshops would change PCPs diagnostic capabilities. This included training on the use of neuropsychological testing and on a battery of cognitive screening tests (the Short Cognitive Evaluation Battery, Robert et al. 2003). There was a two hour educational meeting on Alzheimer's disease and other forms of dementia for groups of doctors. The study failed to show an improvement in detection rates in the intervention group as compared to the controls.

Vollmer and colleagues (2010) investigated whether 'blended learning' methods, (a combination of traditional teaching, e-learning and use of other learning media), would improve GPs knowledge of the diagnosis of dementia. There were two interventions:

- Online learning modules and structured case discussion, covering guidelines on the diagnosis and management of dementia and interactive case stories related to the guidelines.
- Lecture and structured case discussion on dementia.

Participants completed a pre and post knowledge test and test at 6 months. All received a pocket book of the guidelines, and a control group received the printed information only.

They found that both the blended learning and the more traditional methods improved knowledge in these areas, but there was no significant difference between the intervention groups. The control group showed significantly less knowledge gain. A sub-group analysis showed that when GPs self-reported as having used the e-learning modules, their gain was significantly better than the other group's (an increase in knowledge score of 1.17, 95% CI 0.20 to 2.14, p=0.019).

Perry and colleagues (2008) conducted a randomised controlled trial to test home assessments using the EASYcare instrument. This tool assesses activities of daily living, mood, cognition, and has elements of goal setting. The tool was used by geriatric specialist nurses during home visits, triggered by GP referral to the study. Patients were randomised to the intervention or the control. Results showed that dementia diagnosis was significantly improved in the intervention group (29% compared with 9%, p=0.02).

Waldorff and colleagues (2003) attempted to improve adherence to guidelines on diagnosing dementia in a variety of ways:

- Seminars on specific clinical practice guidelines and screening tools, brain imaging as a diagnostic procedure and pharmaceutical treatments for dementia
- Three reminder letters covering the main recommendations in the clinical practice guidelines
- An individualised small-group educational programme
- Outreach visits by a trained GP facilitator, who underwent a 5 hour symposium of training

The study found that there was no significant difference between intervention and control groups in the number of diagnostic evaluations undertaken, the number of investigations ordered, or the number of cognitive tests performed. However, a limitation of this study is that the interventions were delivered to individual GPs but the outcomes were measured at practice level.

Koch and Iliffe (2010) concluded that decision support software, practice based workshops and in-home assessment by nurses increased detection rates. Other strategies improved knowledge about diagnosis and management, more generally. However, they sounded a note of caution by noting the poor quality of some studies, for example the limiting nature of small sample sizes, and the risk of selection bias.

6.8 Types of Delay

6.8.1 Patient Delay
Patients may delay going to the doctor for fear of the stigma of mental illness associated with a diagnosis, and the resultant loss of independence. Patients and their families may not recognise early symptoms of dementia, or may have got used to compensating for their relatives cognitive deterioration. There was a perception that there were few treatment options for dementia, so early diagnosis was not desirable.

6.8.2 Doctor Delay
Therapeutic nihilism was also exhibited by doctors, who were reluctant to initiate investigations as they were uncertain about what support might be available to patients or what they might offer in support by way of treatment or services. Diagnosing dementia in its early stages was judged to be difficult as symptoms were fluctuating and non-specific. PCPs wished to have more education about what constitutes 'normal ageing' so they were able to make accurate diagnoses. They expressed discomfort at using diagnostic tests and wanted greater support and input from specialist colleagues in secondary care. There were communication issues, with difficulties in disclosing and explaining a diagnosis of dementia. Two studies in Bradford et al. (2009) suggested that frequency of contact with a GP assisted diagnosis.

6.8.3 System Delay

Resource constraints hindered early detection. The time of a typical visit to a doctor's surgery did not allow for the completion of diagnostic tests, for example. There were limitations placed on the use of diagnostic tools and on dementia care. Doctors also felt discouraged by the low reimbursement for dementia care.

6.9 Discussion

With regard to the diagnosis of dementia, most delay seems to occur in primary healthcare, either because the patients are delaying in presentation, or primary care physicians are reluctant or unable to make a diagnosis. None of the reviews estimated the average time intervals for any particular stage of the diagnostic process. The lack of delay in secondary care is, in part, due to dementia being a condition most commonly diagnosed and managed in primary healthcare systems. Koch and Iliffe (2010) reviewed mainly educational interventions to improve the detection of dementia and concluded that some interventions were useful, but larger, more robust trials were needed.

6.10 References

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7. Depression

By 2020 it is estimated that depression will become the second leading cause of disability (Murray and Lopez 1997), so the recognition and treatment of the disease has become increasingly important. Research has shown that less than half of depressed patients are recognized as having depression by their GPs, even after a 5 year follow-up (Jackson et al. 2007). Late recognition may lead to poor outcomes, increased service use and higher mortality rates for these patients (Davidson and Meltzer-Brody 1999).

7.1 Overall Summary of Findings

GPs and other non-psychiatric physicians were more likely to recognise people who did not have depression, than identify those who had the condition.

The evidence suggested that older people may be less likely to be diagnosed.

The milder stages of the disease were more difficult to recognise.

7.2 Included Studies

We found three reviews that examined late diagnosis in relation to depression (Cepiou et al. 2007, Das et al. 2006, Mitchell et al. 2011). Cepiou et al. (2007) described and summarised quantitatively data on recognition of depression by non-psychiatric physicians. Das et al. (2006) investigated patient, physician, and practice-setting barriers to the treatment of major depression among African American in US primary-care. Finally, Mitchell et al. (2011) sought to quantify the rate of distress in primary care and to clarify the ability of GPs to indentify distressed or mildly depressed individuals using their clinical skills. Due to the fact the review conducted by Das et al. (2006) has limited relevance to the UK healthcare system, the findings of this review are not discussed further here. The characteristics of the reviews are presented in table 7.1.

None of the primary studies appearing within Cepiou et al. (2007) appeared in Mitchell et al. (2011).

Number of contributing reviews: 3

Table 7.1: Characteristics of Included Studies

Systematic Review [AMSTAR score]	No. of included studies	Pooled no. of participants	Countries	Participants	Disease state
Cepiou et al. 2007 [9/11]*	36	59,978	Not reported	Adult patients attending primary care facilities, hospital emergency departments or outpatient clinics, or admitted to hospital in either medical or surgical wards.	For a paper to be included, the diagnosis of depression had to be made by: • A study psychiatrist or research staff, using a structured clinical interview or a rating scale with a specified cut point (gold standard). • a non-psychiatric physician (or other method of recognition, such as antidepressant prescription, referral to a mental health specialist, or identification of depressive symptoms) (clinical diagnosis).
Das et al. 2006 [4/11]	24	>13,842	US only	Articles were excluded if they did not focus on adult African Americans with depressive disorders in clinical settings within the US.	Not reported.

Systematic Review [AMSTAR score]	No. of included studies	Pooled no. of participants	Countries	Participants	Disease state
Mitchell et al. 2011 [7/11]*	21	35,980 Distress studies - 13,993 Mild depression - 21,987	Not reported	Not reported	Individuals meeting criteria of a depressive episode but with 4 or 5 symptoms are defined as mild depression in ICD10. In DSMIV mild major depression is defined as those with symptoms barely meeting the criteria for major depression and result in little distress or interference with the patient's ability to work, study or socialize. Those with core symptoms not fulfilling full criteria are labelled with minor depression. The definition of distress has not been robustly operationalized in ICD10 or DSMIV. Distress refers to significant emotional upset that is common to a range of psychological and psychiatric conditions.
This review satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool.					

7.3 Prevalence

Cepiou et al. (2007) investigated the sensitivity and specificity of the recognition of depression by non-psychiatric physicians. The majority of these doctors were family practitioners or GPs (18 studies), but there were four studies that concentrated on emergency physicians, and the rest of the studies examined a broad range of medical disciplines or failed to specify the type of doctor involved (four studies).

After combining the results from all 36 included studies, they found high specificity (83.7%, 95% CI: 77.5 to 90.0), but lower sensitivity (36.4%, 95% CI: 27.9 to 44.8), with a resulting diagnostic OR of 4.0 (95% CI: 3.2 to 4.9). The overall sensitivity, calculated by using receiver operating characteristic (ROC) curves, was 42.3%. This means that physicians were usually able to identify individuals who did not have depression, but identified less than half of those who did have the condition.

As a result of carrying out meta-regression on variables associated with sensitivity, they were able to detect three factors that effected sensitivity, namely the method of documentation (physician diagnosis *vs* chart review), age (55 and over *vs* all ages and younger patients only) and date of publication (after 1998 *vs* 1998 and before).

Their calculations showed that the correct diagnosis was more likely to occur if the physician interviewed or tested the individual directly rather than reviewing their case notes (p=0.004); if the patient sample was all ages or younger individuals (p=0.039) or if the paper on which the calculation was based was published after 1998, suggesting that doctor education had improved over time (p=0.024). Only age and date of publication explained the heterogeneity of the pooled odds ratio, meaning that studies that were published after 1998 and had a sample of younger or all ages of patients reported higher odds ratios of recognition compared to studies that were published in 1998 or before and had a sample of patients aged 55 and more. Finally, the researchers conducted a multivariate meta-regression, and found that only method of documentation remained, after controlling for age and publication date, as an explanatory variable for summary sensitivity (p=0.038).

Mitchell et al. (2011) examined the ability of GPs to diagnose distress and mild depression. They calculated the prevalence rate for distress and mild depression (presented in table 7.2), and then investigated the sensitivity and specificity of the diagnosis of these conditions by GPs.

Table 7.2: Prevalence rates for distress and mild depression

Condition	No. of studies	Sample Size	Prevalence (adjusted by meta-analytic weighting)
Distress	16	13,993	44.1% (95% CI=34.7% to 53.8%)
Mild depression	5	21,987	10.6% (95% CI=67.7% to 0.15.1%)

As with Cepiou et al. (2007), Mitchell and colleagues found that GPs were better at identifying those not suffering from distress or mild depression (table 7.3).

Table 7.3: Percentage of individuals correctly identified with or without distress or mild depression

Condition	% of people correctly identified with condition (sensitivity)	% of people correctly identified without condition (specificity)
Distress	48.4% (95% CI=42.6% to 54.2%)	79.4% (95% CI=74.3% to 84.1%)
Mild depression	33.8% (95% CI=27.3% to 40.7%)	80.6% (95% CI=66.4% to 91.6%)

After Bayesian comparison, Mitchell and colleagues found that physicians were more accurate in their ability to rule in distress ($AUC_{distress}$ 0.639; 95% CI 0.631 to 0.647) than mild depression (AUC_{mild} 0.59; 95% CI 0.571 to 0.611), but they were most successful at identifying moderate or severe depression ($AUC_{non\text{-}mild}$ 0.670; 95%CI0.656to0.684). There was the same trend in their abilities to rule out these conditions.

Mitchell and colleagues then examined misclassification rates (see table 7.4 below), calculating the number of true identifications made by a typical GP by using a corrected positive predictive value (PPV) of 60.5% (95% CI 59.0% to 61.9%) for mild depression and 17.1% (95% CI 14.8% to 19.9%) for mild depression, and a corrected negative predictive value of 70.3% (95% CI 69.3% to 71.1%) for distress and 91.1% (95% CI 90.0% to 92.0%) for mild depression.

Table 7.4: Misclassification rates

Condition	Pooled prevalence	No. of correct identifications with the condition (out of 100 cases)	No. of missed diagnosis (out of 100 cases)	No. of correct reassurances (out of 100 cases)	No. of false diagnoses (out of 100 cases)	% of correct identifications	Misclassification rate
Distress	39.4%	19	20	48	13	66%	33%
Mild depression	10.6%	4	7	72	19	76%	24%

Both reviews had few comments about the quality of the primary studies. Cepiou et al. (2007) admitted to difficulties in forming an opinion about the quality of the papers because of the variability of methods used. In order to offer a view about the methodological quality of the studies that may have affected the validity of their results, they presented data on method of sampling, sites of the studies, blinding of outcomes and the specialities of the doctors involved. Mitchell et al.

(2011) limited the majority of their analysis to the 16 studies on distress and five on mild depression that reported sensitivity and specificity rates. They also acknowledged that the definition of distress has not been robustly operationalized in psychiatric diagnostic manuals DSMIV or ICD10.

7.4 Determinants

There was no information about determinants of delay in these reviews.

7.5 Outcomes

There was no information about outcomes of delay in these reviews.

7.6 Cost Implications

There was no information about the cost implications of delay in these reviews.

7.7 Interventions

There was no information about interventions to reduce delays in these reviews.

7.8 Types of Delay

7.8.1 Doctor Delay
Both reviews showed that GPs and others were more able to identify true negatives, i.e. those without the condition, in relation to depression, mild depression and distress. Their ability to recognise individuals suffering from these conditions was less apparent, with Cepiou et al. (2007) calculating an overall sensitivity of 42.3%, meaning that non-psychiatric physicians recognised less than 50% of sufferers. This was particularly the case with older people, although their analysis suggested that sensitivity generally had improved over time.

Mitchell et al. (2011) found that doctors were most likely to recognise moderate depression, and least likely to identify sufferers with mild depression. They questioned the usefulness of diagnosing distress or mild depression as often these conditions improved without any medical intervention. However, treatment of the mild stage of depression may prevent transition to more serious stages.

7.9 Discussion

Our findings echo the NICE guidelines which have cited studies suggesting that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient–doctor relationship and it is the milder forms, which are more likely to recover spontaneously, that go undetected and untreated (National Institute for Health and Clinical Excellence, 2010).

Attempts to improve recognition and diagnosis of depression in primary care are reflected in the Quality and Outcomes Framework (QOF) indictors of the GP contract. Quality Indicator DEP 1 encourages the screening of patients by making a record of the percentage of patients with diabetes and/or heart disease for whom case finding for depression has been undertaken on one occasion during the previous 15 months (NHS Evidence Clinical Knowledge Surveys, 2009). Recently,

there has also been more focus on recognition by clinicians in acute hospital settings with an emphasis on co-morbidities, which (with respect to long-term conditions) most commonly include depression and dementia (personal communication via email 20.06.12, from Dr Hugh Griffiths, National Clinical Director for Mental Health).

The Improving Access to Psychological Therapies (IAPT) programme which supports the implementation of National Institute for Health and Clinical Excellence (NICE) guidelines for people suffering from depression and anxiety disorders anticipates that by 2015 a nationwide roll-out of psychological therapy services for adults will be completed, a stand-alone programme for children and young people will be initiated, and models of care for people with long-term physical conditions, medically unexplained symptoms and severe mental illness will be developed, with estimated savings of up to £272 million for the NHS and £700 million for the public sector (IAPT 2012).

7.10 References

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8. Type I Diabetes

Diabetic ketoacidosis carries a risk of life-threatening complications and is the most common cause of diabetes-related death in children. Presenting in diabetic ketoacidosis may be used as a proxy for delayed diagnosis in type I diabetes. However, it should be noted that diabetic ketoacidosis may also result as a consequence of acute onset of disease.

8.1 Overall summary of findings

Four studies within Usher-Smith et al. (2011) reported a substantial proportion (16-51%) of children experiencing delayed diagnosis (>24 hours for any reason).

Children aged five years or less, from an ethnic minority or having parents with lower educational or socio-economic status were more likely to present with diabetic ketoacidosis. One study showed that girls were more likely to experience a delayed diagnosis but did not have an increased risk of severe diabetic ketoacidosis.

A delay of more than 24 hours between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with a four-fold increased risk of presenting with diabetic ketoacidosis.

One multicentre study included within Usher-Smith et al. (2011) showed that across Europe a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of diabetic ketoacidosis in children.

8.2 Included studies

We found one systematic review relating to delayed diagnosis in type I diabetes (Usher-Smith et al. 2011). Usher-Smith and colleagues examined factors associated with the presence of diabetic ketoacidosis at diagnosis of new onset, previously undiagnosed type I diabetes in children and young adults. The characteristics of this review are presented in Table 8.1 below.

Number of contributing reviews:1

Table 8.1: Characteristics of the systematic review investigating diabetic ketoacidosis in children and young people presenting with type I diabetes

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Usher-Smith et al. (2011) (11/11)*	46 cohort studies	>24,000	US (7)(n=2181) Poland (5) Finland (4) (n=3002) UK (4) Austria (1)(n=3471) Germany (3) (n=2533) Italy (3) Sweden (3) (n=2304) Kuwait (2) Saudi Arabia (2) Bosnia and Herzegovina Bulgaria (1) Canada (1)(n=3947) Chile (1) China (1) Europe (1) France (1) Ireland (1) Lithuania (1) Oman (1) Taiwan (1) Turkey (1)	Children and young adults (0-21 yrs) presenting with new onset type 1 diabetes	Definitions of diabetic ketoacidosis included either pH values of ≤7.2 to <7.36 or bicarbonate values of <15 to ≤21 mmol/L
This review satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool (see Appendix 2).					

8.3 Prevalence

Four studies within Usher-Smith et al. (2011) explored the impact of delayed diagnosis (delay >24 hours for any reason) on the development of diabetic ketoacidosis. All reported a significant proportion (16–51%) of children experiencing delay, but it was not possible to combine data due to different definitions used.

8.4 Determinants

Each determinant is accompanied by the number of contributing studies (n) and where possible, we have noted positive (+), negative (-), or no (□) association with late referral. Associations are statistically significant unless indicated non-significant (NS).

The determinants of presenting with type I diabetes and diabetic ketoacidosis are presented in Table 8.2 below.

Table 8.2: Factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults.

Determinants	Usher-Smith et al. (2011) No. of primary studies (n); Association with diabetic ketoacidosis: Positive +(more likely); Negative – (less likely); None □ (no association)
Demographic	**Age:** <2 years old (4+) ≤5 years old (7+), (7 +NS), (1 □), (1 – NS) **Gender:** Female (20 □) (1 + NS) **Ethnicity** Ethnic minority (5+) **Parental Education (3+)** Lower parental education (3+) **Family Structure (3 □)** Living in a single parent family/no. of children in family (3 □) **Rural vs Urban Residence** Living in rural vs urban areas (3 □) **Socio-economic status (3+) (3□)** Family income (Europe) (2 □) Family in the two lowest quintiles of family income (Canadian study)(1 +) Mother unemployed (Sweden) (1 +) Father's employment status (Lithuania) (1□) Parents in social classes 3–5 *vs* those in social classes 1 and 2 (UK) (1+)
Medical	**Family History** First degree relative with type 1 diabetes (3-)(1□) Family history (1□). Second affected child *vs* first affected child (1-) **Body Mass Index:** Lower BMI (2+) **Duration of symptoms:** Shorter duration of symptoms (2+) Duration of classic symptoms (1□) **Pattern and frequency of symptoms:** Frequency of typical symptoms (enuresis, nocturia, polyuria, polydipsia)(1□); Vomiting, abdominal pain, dyspnoea, weakness, anorexia, mental changes (1+); Greater weight loss (2+) (1□) **Comorbidities:** History of infection or febrile illness (2+)(1□)

Determinants	Usher-Smith et al. (2011) No. of primary studies (n); Association with diabetic ketoacidosis: Positive +(more likely); Negative – (less likely); None □ (no association)
	Rarity of condition: Lower background incidence (1+)
System	**Presence of structured diabetes team** Hospitals lacking a structured diabetes team (Kuwait) (1+)

Determinants: Key Findings

Demographic

- Age: Children <2 years old had three times the risk of presenting in diabetic ketoacidosis as children aged ≥2 years (OR 3.41, 95% CI 2.54 to 4.59, p<0.001, I^2=21.1%) and this association continued up to age 5 (OR 1.59, 95% CI 1.38 to 1.84, p<0.001, I^2=23.5%).

- Gender: Twenty studies showed that gender was not associated with the risk of presenting in diabetic ketoacidosis. A multivariate analysis of 262 children showed that, although female sex was significantly associated with increased risk of delayed diagnosis (symptomatic period ≥4 weeks) (OR 2.78, 95% CI 1.09 to 7.14, p=0.033), it was not associated with an increased risk of severe diabetic ketoacidosis (OR 0.68, 95% CI 0.26 to 1.83).

- Ethnicity: it was not possible to determine whether the frequency of diabetic ketoacidosis was significantly different in any ethnic group. However, five studies showed that ethnic minority groups experienced an increased risk of diabetic ketoacidosis: In the US Non-Hispanic White *vs* Others (OR 0.55, 95% CI 0.32 to 0.96), White people *vs* Hispanic (OR 0.33, 95% CI 0.14 to 0.76),Non-Hispanic White *vs* Hispanic (OR 0.58, 95% CI 0.37 to 0.89) and in the UK White *vs* Others (OR 0.39, 95% CI 0.15 to 0.98) Non-Asian *vs* Asian (OR 0.35, 95% CI 0.18 to 0.66).

- Parental education: Having a mother with higher than secondary education was protective against developing diabetic ketoacidosis in Lithuania (OR 0.4, 95% CI 0.20 to 0.79). A similar effect was observed by having at least one parental academic degree in Finland (OR 0.64, 95% CI 0.43 to 0.94). A German study presented a multivariate analysis showing that children with parents with ≤9 years of education were more likely to develop severe diabetic ketoacidosis than children with parents with ≥12 years education (OR 3.54, 95% CI 1.10 to 11.35, p= 0.034).

- Family structure: Three studies examining family structure found that neither number of siblings nor single parent status were associated with the risk of developing diabetic ketoacidosis (OR 1.85, 95% CI 0.43 to 7.82, p=0.411).

- Rural/ Urban Residence: Three studies from Sweden, Finland and Lithuania respectively, found that there was no association between rural vs urban living and the risk of developing diabetic ketoacidosis.

- Socio-economic status: Two European studies found that family income had no significant effect on risk of presenting in diabetic ketoacidosis. A Canadian study, which adjusted for age and sex, showed that being from a family in the two lowest quintiles of family income was associated with an increased risk of diabetic ketoacidosis (OR 1.38, 95% CI 1.17 to 1.63).In Sweden having an unemployed mother significantly increased the risk of presenting in diabetic ketoacidosis (OR 4.8, 95% CI 1.8 to 13.1), while in Lithuania father's employment status had no effect on the rate of diabetic ketoacidosis (OR 1.17, 95% CI 0.53 to 2.57). One study from the UK reported that children with parents in social classes 3–5 *vs* social classes 1and 2 were more likely to present in diabetic ketoacidosis (p<0.05).

Medical

- Family History: A small retrospective UK study showed that children who were second affected in a family were less likely to present in diabetic ketoacidosis than first affected children (OR 0.07, 95% CI 0.003 to 1.51, n=79). Three studies showed that having a first degree relative with type I diabetes decreased the frequency of diabetic ketoacidosis, however a US study did not predict a diagnosis of diabetes before onset of diabetic ketoacidosis after adjusting for age, sex, diagnosis in primary or secondary care, and duration of symptoms. A German study which adjusted for age, sex, single parent and social status also failed to show a significant association with a family history.

- Body Mass Index: Two studies showed a higher frequency of diabetic ketoacidosis in those children with a lower BMI.

- Duration of symptoms: Two studies found that children with diabetic ketoacidosis had shorter duration of symptoms (p<0.005), but the proportion of children with symptoms <2 weeks did not differ between the groups (p=0.80). A further study showed that after adjustment for age, sex, family history and diagnosis in primary or secondary care, the duration of classic symptoms (enuresis, nocturia, polyuria, polydipsia, appetite, weight loss, candidiasis and fatigue) failed to predict a diagnosis of diabetes before onset of diabetic ketoacidosis.

- Symptom pattern and frequency: One study found no difference in the frequency of any of the typical symptoms of diabetes between children with and without diabetic ketoacidosis. However, other studies provided contradictory evidence, finding that children with diabetic ketoacidosis presented more often with vomiting (n=3), abdominal pain (n=2) and dyspnoea (n=1). One study found that weakness, anorexia, and changes in mental status were more frequent in children presenting with diabetic ketoacidosis. Two studies showed that children with diabetic ketoacidosis had significantly greater weight loss than those without (p<0.005), while a third study showed no difference (p=0.296).

- Co-morbidities: Two studies reported that a history of febrile illness was associated with an increased risk of diabetic ketoacidosis (OR 6.50, 95% CI 2.06 to 20.53; and 1.87, 95% CI 1.05 to 3.33 respectively). One study reported febrile illness as more common in groups with shorter duration of symptoms (<1 month), but this did not change the percentage with severe ketoacidosis.

- One multicentre study using data from 11 centres across Europe showed a significant inverse correlation between the proportion presenting with diabetic ketoacidosis and the background incidence of type I diabetes for these centres (*r*s = –0.715, p=0.012).

System

- One Kuwaiti study, which may have limited relevance to the UK healthcare system, found that diabetic ketoacidosis was significantly more common in hospitals lacking a structured diabetes team (p<0.002).

8.5 Outcomes

8.5.1 Referral/diagnosis:

Four studies within Usher-Smith et al. (2011) examined the effect of delayed referral upon the risk of presenting with diabetic keotacidosis.

Delay >24 hrs between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with a four-fold increased risk of presenting with diabetic ketoacidosis (52.3% v 20.5%, p<0.05, OR 4.26, 95% CI 1.54 to 11.79).

A similar increase in risk occurred in children who were not diagnosed on the day of admission to a US children's hospital (59% (17/29) v 33% (35/105), p=0.0178, OR 2.83, 95% CI 1.22 to 6.58)).

Two European studies found no effect when there was a delay between first medical consultation and hospitalisation (OR 0.79, 95% CI 0.31 to 2.00) or delay of >24 hrs between first visit and diagnosis (OR 0.98, 95% CI 0.73 to 1.31).

8.5.2 Treatment:

One multicentre study included within Usher-Smith et al. (2011) showed that across Europe a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of children developing diabetic ketoacidosis (OR 1.74, 95% CI 1.10 to 2.77).

8.6 Costs Implications

The cost implications of presenting with diabetic ketoacidosis were not examined.

8.7 Interventions

No interventions were described or evaluated within the included systematic review.

8.8 Types of delay

None of the studies within this review estimated the average time intervals for any particular stage of the diagnostic process. Nor did this review examine any aspect of patient delay.

8.8.1 Doctor delay

8.8.1.1 Diagnostic error
Children not diagnosed on their first visit, either due to misdiagnosis or signs and symptoms missed /not recognised, had a threefold increased risk of presenting in diabetic ketoacidosis (combined OR 3.35, 95% CI 2.35 to 4.79, p<0.001, I^2=0%). Risk was independent of presence or absence of infection preceding diagnosis, but diagnostic error was significantly more likely to occur in younger children: the mean age of children who presented with diabetic ketoacidosis was 5.4 (SE 4.4) years when the diagnosis was missed compared with 8.8 (SE 4.0) years when the diagnosis was not missed (p<0.001).

8.8.1.2 Number of consultations before diagnosis
Two studies within Usher-Smith et al. (2011) reported the number of medical consultations that occurred before the diagnosis of diabetes.

A Canadian study found that 84% of 247 children had been seen in primary care before referral to secondary care: 66% on the day of diagnosis, 14% once, and 4% at least twice before the date of diagnosis. However, the number of visits did not differ between children with and without diabetic ketoacidosis (p=0.30).

A US study found that significantly more children presenting with diabetic ketoacidosis had one or more medical consultations in the week before diagnosis (38.8% (285/735) *vs* 34.4% (1104/3212), p=0.026).

8.8.2 System delay
One multicentre study included within Usher-Smith et al. (2011) showed that across Europe a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of children developing diabetic ketoacidosis (OR 1.74, 95% CI 1.10 to 2.77).

8.9 Discussion

Four studies within the included systematic review reported a substantial proportion (16–51%) of children experiencing delayed diagnosis in type I diabetes (>24 hours for any reason). Notably, younger age and belonging to an ethnic minority were associated with presenting with diabetic ketoacidosis at diagnosis of type I diabetes in children and young adults. Delay >24 hours between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with a four-fold increased risk of presenting with diabetic ketoacidosis.

Early diagnosis of type 1 diabetes may be difficult to improve upon due to aggressive onset of disease. Unfortunately, the focus of the included review was specifically upon the determinants of delay, and thus no interventions to reduce delays in diagnosis were examined. However, an Italian study has demonstrated that the incidence of diabetic ketoacidosis in newly diagnosed diabetic children aged 6–14 years was reduced, in the area of Parma, eight years after an information program on diabetic ketoacidosis was introduced to teachers, students, parents, and paediatricians (Vanelli et al. 1999). Diabetic patients diagnosed in the

Parma area (n=24) were compared with those patients coming from two nearby areas in which no campaign had been carried out (n=30). Diabetic ketoacidosis was diagnosed in 3 children (12.5%) of the intervention group, compared with 24 (83%) of the comparison group. The duration of symptoms before diagnosis was 5.0 ± 6.0 days in the intervention and 28.0 ± 10.0 days (p < 0.0001) in the comparison group. The total cost of the 8-year campaign, initiated in 1991, was $23,470.

Further information regarding the determinants of delayed diagnosis and opportunities for improving the time to diagnosis of type I diabetes may be provided by as yet unpublished data from the Early Care Survey, conducted in the UK. The newly-established regional paediatric diabetes network system and the Association of Children's Diabetes Clinicians has been used to gather approximately 250 responses over a three month period in this national audit of the pre-hospital experience of parents of children newly diagnosed with diabetes. The influence of factors including family structure, parents' educational level and socio-economic status upon delays to diagnosis (and the development of diabetic ketoacidosis) are being examined. Results from the audit will be available in late 2012 (Personal communication via email on 2nd May 2012 from Dr Julie Edge, Consultant in Paediatric Diabetes, Oxford Children's Hospital).

8.10 References

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Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacolone T, Chiarelli F (1999) Effectiveness of a prevention program for diabetic ketoacidosis in children: an eight year study in schools and private practices. *Diabetes Care* 22: 7–9.

9. Epilepsy

Making a diagnosis of epilepsy can be difficult, and so misdiagnosis is a frequent occurrence, happening in about 25% of cases (Scheepers et al. 1998, Smith et al. 1999). To reach an accurate diagnosis of epilepsy, a clinician needs to differentiate between seizures and other causes of temporary neurological disturbance, such as syncope, and between acute symptomatic seizures that are part of another acute mental illness and unprovoked epileptic seizures (Stokes et al. 2004). There are various types of epilepsy and it is important to identify the specific type in order to provide the appropriate treatment and information about prognosis (Stokes et al. 2004).

We found two reviews that examined the impact of misdiagnosis of epilepsy (Chapman et al. 2011, Juarez-Garcia et al. 2006), rather than the late diagnosis of epilepsy. This misdiagnosis will result in the late diagnosis of another condition but not epilepsy. We then examined the primary studies for late diagnosis of epilepsy in the UK, and found a similar pattern of misdiagnosis reported, with a little more information about the prevalence and outcomes of late diagnosis. In this chapter, we discuss the primary studies (Beach and Reading 2005, Bhatt et al. 2004, Brodie and Stephen 2007, O'Callaghan et al. 2011).The characteristics of the two systematic reviews are presented in Section 9.8 at the end of this chapter.

9.1 Overall summary of findings

The four primary studies provided very limited information about late diagnosis. However, experts recognize that it is a problem, related, partly, to late presentation. It is possible that over-diagnosis may present a more significant problem for this condition in adults.

In a UK national study, 27% of infants suffering from infantile spasms had a lead time to treatment of over two months.

Late treatment may contribute to developmental delay in children, and, in older patients, to an increased likelihood that the sufferer would not become seizure free after treatment.

One hospital managed to increase reduced the number of undetermined cases of epilepsy via case review and checks by independent neurologists.

9.2 Included Studies

There were four primary studies: Beach and Reading (2005) conducted a case review in a district hospital to improve the accuracy of epilepsy diagnosis; Bhatt et al. (2005) carried out an audit of emergency cases in a London hospital to track the management of possible epilepsy patients; Brodie and Stephen (2007) analysed clinical data in a prospective cohort study from older patients attending an epilepsy clinic; and O'Callaghan et al. (2011) investigated the effect of lead time to treatment on developmental outcomes for children suffering from infantile

spasms, a form of epilepsy. The characteristics of the studies are presented in table 9.1.

Table 9.1: Characteristics of included primary studies

Study / year [Quality grade]	Research Design	Region	Participant Characteristics	Disease state / condition
Beach and Reading 2005 [medium]	Case review	Norfolk	Sample: 684 children Age: between 29 days and 16 years.	Epilepsy: a diagnosis of epilepsy made on the basis of clinical history or records, sometimes with confirmatory investigations. Possible epilepsy: at presentation there were features suggestive of epilepsy, but insufficient evidence to make a confident diagnosis. Non-epileptic events: attacks confidently diagnosed as one of the recognised non-epileptic conditions of childhood. Febrile seizures: seizures complicating febrile illnesses in children under 6 years and over 6 months of age. Isolated epileptic seizures: an unprovoked single epileptic seizure or cluster of epileptic seizures during a 24 hour period. Acute symptomatic epileptic seizures: seizures complicating an acute medical illness where the cause could be identified.
Bhatt et al. 2004 [medium]	Case review	London	Sample: 38 patients presenting to an A&E department	Unclear. Clinical diagnosis confirmed by MRIs and EEGs.
Brodie and Stephen 2007 [medium]	Cohort study	Glasgow	Sample: 90 patients Gender: 53	Diagnoses were made by obtaining witness accounts of epileptic events whenever

| | | | men, 37 women
Age: median 73 years (range 65 – 93)

88 patients (98%) with partial or secondary generalized seizures
2 patients (2%) with alcohol withdrawal seizures | possible. Most patients underwent routine brain neuro-imaging; electroencephalography was undertaken to aid seizure and syndrome classification in some cases. Additionally, prolonged electrocardiographic recording, carotid and basilar ultrasound, orthostatic blood pressure measurements, tilt testing and hematological, biochemical and thyroid profiles were ordered. |
| O'Callaghan et al. 2011

[medium] | Cohort study | UK | Sample: 77 infant data analysed

Age: between 2 and 12 months | Infantile Spasms: clinical diagnosis of infantile spasms and compatible EEG. |

9.3 Prevalence

Two studies reported on treatment delay, one focussed on infants (O'Callaghan et al. 2011), and one on patients presenting to an accident and emergency department of a London hospital (Bhatt et al. 2005).

O'Callaghan et al. (2011) identified the lead time to treatment for 77 infants with infantile spasms, by asking for the exact date of onset of the ictal manifestations of the spasms from clinicians. Where this was not known, the age at onset was requested with an indication of its accuracy to the nearest week or month. The researchers distinguished those infants with a proven aetiology (39) from those with no identified aetiology (37). Just over a quarter (27%) of infants were treated over 2 months after the first spasm occurred. There was little difference between the categories in terms of lead time to treatment, with the longest intervals of >2 months recorded for 10 infants (proven aetiology) and 11 infants (no identified aetiology). Full results are given in table 9.2.

Table 9.2: Time to treatment for infants with infantile spasms

Lead time to treatment	All infants	Proven aetiology	No identified aetiology
< 8 days	11	5	6
8-14 days	17	10	6
15 days to 1 month	8	3	5
1 – 2 months	15	8	7
>2 months	21	10	11
Not known	5	3	2
Total number	77	39	37

Bhatt and colleagues carried out a short 6 month case review of patients presenting with 'first fit' as an emergency case at a district hospital. They reviewed 38 cases, 24 of which were discharged and 14 admitted. Twelve patients were sent home with a letter for their GP requesting a neurology referral, but only two were subsequently seen at the clinic, while of those directly referred to a neurologist, two were lost to follow up. There was no clinical difference between those patients referred directly and those discharged with a GP letter. Patients (n=10) waited a median waiting time of 22 weeks to be seen by a neurologist for a review, 18 weeks longer than recommended. The mean average interval for patients (n=8) between the clinic visit and an MRI scan and EEG were 12 and 15 weeks respectively. The MRI interval met the suggested time interval, but EEG interval was 11 weeks longer than recommended.

9.4 Determinants

There was no information about the determinants of delay.

9.5 Outcomes

Two primary studies reported on outcomes associated with late diagnosis. Brodie and Stephen (2007) investigated the effects of treatment delay on older people attending an epilepsy clinic after their first fit, and O'Callaghan et al. (2011) looked into the effects of treatment delay on developmental scores at 4 years for infants (=/< 10 months) with infantile spasms.

In the cohort study conducted by Brodie and Stephen (2007), it was found that patients who began treatment two or more years after experiencing their first seizure were less likely to gain full seizure control than those patients who began treatment closer to the onset of epilepsy (89% seizure freedom for those with <2 years since first seizure v. 70% seizure freedom for those with >2 years since first seizure, $p<0.05$). It is unclear whether the delay is treatment or patient delay.

O'Callaghan and colleagues found that, after controlling for the effects of treatment and aetiology, there was a significant association between development scores on the Vineland Adaptive Behaviour Scale at 4 years and lead time to treatment [regression coefficient (SE) -3.9 (1.7), $p=0.03$], showing that for each increase in each lead time category, (see table 9.2), there was a drop in developmental quotient by 3.9 points.

9.6 Cost Implications

There was no information about the cost implications of delay.

9.7 Interventions

Beach and Reading (2005) reported on a study that aimed to ascertain the diagnosis of epilepsy on children attending a district hospital over a two year period. For all children aged between 29 days and 16 years presenting with definite or possible seizures or paroxysmal disorders, a case review was carried out by main author, and then to check the accuracy of the diagnostic classification, a random sample was reviewed independently by two neurologists.

During the two years, 684 cases were ascertained. Ninety children were initially classified as 'possible epilepsy' and 61 (66%) were thereafter reclassified because of further information from attack descriptions, natural history or investigation results. Of the 61 reclassifications, 31 were diagnosed with epilepsy. Twenty nine children remained uncertain, and six of these had absent or doubtful histories. After 6 – 30 months of follow up, 21 of the children had been discharged with a final diagnosis of possible epilepsy, and eight were still under review.

The 'possible epilepsy' cases reviewed independently resulted in a variety of responses but no unanimity; however, there was always one neurologist in agreement with the study diagnosis.

9.8 Types of Delay

9.8.1 System Delay
The study from Bhatt et al. (2005) suggested that there were some system delays for patients presenting with a 'first fit' to an accident and emergency department, and many more who were discharged with a letter for a GP to request a referral were lost to follow up, than those directly referred to a neurology clinic. They recommended that all 'first fit' patients were directly referred.

9.9 Discussion

The diagnosis of epilepsy is difficult and as Beach and Reading (2005) reported and even neurologists can disagree on individual cases. However, O'Callaghan and colleagues were able to demonstrate that infantile spasms can have serious developmental impacts on young children, and so diagnostic suspicion of epilepsy in infants in primary care has important consequences, although a GP may have to work for an average of 300 years before they see a case (O'Callaghan et al. 2011).

The older patients in Brodie and Stephen's (2007) study were not given medication after their first fit, unless it was obviously due to epilepsy, and encouraged to come back to the clinic if they suffered a second fit. Recurring seizures increase confidence that the diagnosis is epilepsy, rather than a non-epileptic event, but the study showed that the longer the time from the first fit episode, the more likely it was that the patient would not experience seizure freedom.

First seizure clinics have been established in several centres to ensure that patients receive the right advice and treatment. It is not considered clinically acceptable for patients to be put on routine waiting list for local neurologists after their first seizure as the opportunity for early intervention will be lost (personal communication from Dr Chris Clough, consultant neurologist, Kings College Hospital).

Recent NICE guidelines, published in 2012, on the diagnosis of epilepsy and training by the British Paediatric Neurology Association may improve the situation for affected children and their families. An audit by the Royal College of Paediatrics and Child Health, due to report in September 2012, may throw further light on the problem of diagnosing epilepsy in children (personal communication from Dr Edward Wozniak, paediatrics advisor, Department of Health).

Both systematic reviews focussed upon misdiagnosis, which appears to be common. This has cost and health implications for patients that are treated inappropriately for a condition they do not have, while the true condition remains untreated. Juarez –Garcia et al. (2006) identified the chief economic burdens of misdiagnosis as inpatient admissions (45%), inappropriate prescribing of antiepileptic drugs (AEDs) (26%), outpatient attendances (16%) and GP care (8%), with an estimated annual medical cost in England and Wales of £29000000, and possible total costs of up to £138000000 a year.

9.10 Characteristics of the Systematic Reviews

Chapman and colleagues analysed data from studies looking at the misdiagnosis of epilepsy in people with intellectual disabilities, while Juarez-Garcia and colleagues calculated the costs of epilepsy misdiagnosis in England and Wales. The characteristics of both reviews are presented in table 9.3

Table 9.3: Characteristics of Included studies

Study [AMSTAR score]	No. of primary studies included	Pooled no. of participants	Countries	Participants	Disease state/condition
Chapman et al. 2011 [10/11]*	8	1363 children and adults	USA (4), Australia (2), Denmark, UK	Children and adults with intellectual disabilities Learning disability nurses	Not reported
Juarez-Garcia et al. 2006 [8/11]	5	835	England and Wales	Adults and children	A correct diagnosis of epilepsy requires that the clinician differentiate between seizures and other causes of transient neurological disturbance and collapse, such as syncope, and between acute symptomatic and unprovoked epileptic seizures.
Those studies marked with an asterix satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool.					

9.11 References

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Bhatt H, Matharu MS, Henderson K, Greenwood R (2005) An audit of first seizures presenting to an Accident and Emergency department. *Seizure* 14: 58-61

Brodie MJ, Stephen LJ (2007) Outcomes in elderly patients with newly diagnosed and treated epilepsy. *International Review of Neurobiology* 81: 253-263.

Chapman M, Iddon P, Atkinson K, Brodie C, Mitchell D, Parvin G, Willis S (2010) The misdiagnosis of epilepsy in people with intellectual disabilities: a systematic review. *Seizure* 20: 101-106.

Juarez-Garcia A, Stokes T, Shaw B, Camosso-Stefinovic J, Baker R (2006) The costs of epilepsy misdiagnosis in England and Wales. *Seizure* 15: 598-605.

O'Callaghan FJ, Lux AL, Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, Verity CM, Osborne JP (2011) The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia* 52: 1359-1364.

Scheepers B, Clough P, Pickles C (1998) The misdiagnosis of epilepsy: findings of a population study. *Seizure* 7: 403-406.

Smith D, Defalla BA, Chadwick DW (1999) The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM* 92: 15-23

Stokes T, Shaw EJ, Juarez-Garcia A, Camosso-Stefinovic J, Baker R (2004) *The diagnosis and management of the epilepsies in adults and children in primary and secondary care*. London: Royal College of General Practitioners, National Collaborating Centre for Primary Care.

10. Human Immunodeficiency Virus (HIV)

Delayed diagnosis of human immunodeficiency virus (HIV) positive status produces patients who are unable to benefit from timely treatment and at risk of transmitting the virus. In the European Union it is estimated that 30% of HIV-infected persons have not been diagnosed (Hamers and Phillips 2008). At the end of 2008 the number of people living with HIV in the UK was estimated to be 83,000, of whom an estimated 27% were unaware of being infected (Health Protection Agency, 2009). Of the 6,658 new HIV diagnoses made in 2010, 50% were late (with a CD4 cell count of <350/mm^3) and 28% very late (with a CD4 count <200 cells/mm^3) (Health Protection Agency, 2011). When including community care costs, HIV treatment costs increased from £164 million in 1997, to £683 million in 2006 and a projected figure of between £1,019 and £1,065 million in 2013 (Mandalia, 2010) .

10.1 Overall summary of findings

Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis.

Fear of disclosure was a barrier to testing among African communities in the UK.

Uptake of testing was inhibited among migrants who thought that HIV status might have a bearing on the immigration process.

GPs were reluctant to discuss HIV testing with patients, even those from high-risk groups, and preferred to refer patients elsewhere for testing.

There was no information about the prevalence, outcome or cost implications of delayed diagnosis of HIV infection, and none of the primary studies within the included reviews examined interventions to reduce delayed diagnosis of HIV infection.

10.2 Included studies

We found two systematic reviews relating to delayed diagnosis of HIV (Chen et al. 2011, Deblonde et al. 2010). Chen et al. (2011) performed a systematic review of the risk of late diagnosis and rate of survival after HIV/AIDS diagnosis among Hispanics compared to other ethnic groups within the United States. Deblonde et al. (2011) conducted a systematic review of barriers to HIV testing in Europe. The characteristics of both reviews are presented in Table 10.1 below.

Number of contributing reviews: 2

Table 10.1: Characteristics of the two systematic reviews

Systematic review [AMSTAR score]	No. Included studies	Pooled no. of subjects	Countries	Participants	Disease State
Deblonde et al. 2010 [8/11]	24	30,368 patients; 38,170 records	UK (15); Netherlands (4); Russia (2); Hungary (2); Italy (1); Switzerland (1); Balkans (1)	14 studies provided information on barriers experienced at clients' or patients' level by incorporating the views of pregnant women, sex workers, men-who-have-sex-with-men (MSM), sexually active youths and migrants. Six studies identified barriers at health care provider level by incorporating the views of GPs, midwives and key informants working in the field of HIV and African communities in the UK, including clinical doctors, health promotion specialists and volunteers. Seven studies identified barriers at institutional or policy levels by incorporating the views of public health officials, prison authorities and directors of drug treatment centres.	Not reported

Systematic review [AMSTAR score]	No. Included studies	Pooled no. of subjects	Countries	Participants	Disease State
Chen et al. 2011 [4/11]	25 of which Delayed diagnosis = 15 Delayed HIV diagnosis = 8; Delayed enrollment in HIV care = 7	391,970 Delayed diagnosis = 343 562 Delayed enrollment = 48404	US only	The majority of studies analyzed all Hispanics as one group, ignoring differences in country of origin, foreign versus US birth, English proficiency, and gender. Of the 15 articles reviewed for delayed HIV diagnosis or enrollment in care, two included only men (one of them only MSM), one included only heterosexually-acquired HIV, and five specifically evaluated foreign-born Hispanics.	*Late HIV diagnosis* The definition of late diagnosis or delayed presentation to care varied from by study. Late presentation was defined as any article that measured concurrent HIV/AIDS diagnosis, time to AIDS, CD4 count on initial presentation, opportunistic infection at HIV diagnosis, and non-early diagnosis of HIV.

10.3 Prevalence

10.3.1 Delayed HIV diagnosis among Hispanic Americans.
In all but one of eight studies, Hispanics had a delayed HIV diagnosis compared to Whites. Centers for Disease Control and Prevention (CDC) data from 1996 to 2001 showed that within 1 year of HIV diagnosis, 46.7% of Hispanics were diagnosed with Acquired Immune Deficiency Syndrome (AIDS) compared to 40.6% of Whites and 39.4% of Blacks (Hall et al. 2007) More recent CDC data (2001–2005) found that over half of all Hispanics were diagnosed late with HIV infection (57.7%) compared to 53.1% of Black and 54.1% of Whites (Hall et al. 2009). Hispanic MSM were diagnosed later than White MSM (24% vs. 18% respectively). Only one study, restricting analysis to heterosexually-acquired HIV, reported similar timing of diagnosis between Hispanics and Whites (Espinoza et al. 2007).

10.3.2 Delayed enrolment in HIV care among Hispanic Americans.
Seven studies reported that Hispanics or immigrants presented to clinical care at a later point, as measured by percent with AIDS or opportunistic infections (OIs), lower CD4 cell count, or faster progression to AIDS or death (Althoff et al. 2010, Carabin et al. 2008, Giordano et al. 2010, Kelley et al. 2007, Levy et al. 2007, Schwarcz et al. 2007, Wohl et al. 2009). In a ten-city study in the US, Schwarcz et al (2010) found that Whites were twice as likely as Hispanics and Blacks to be diagnosed very early (≤ 6 months of infection). Hispanics were more likely to present to care with AIDS or OIs at two of six public health HIV clinics, and the mean CD4 count at presentation was lower among Hispanics compared to non-Hispanics at all sites (Carabin et al. 2008).

10.4 Determinants

Determinants of delayed diagnosis of HIV status, in the form of barriers to HIV testing, are presented in Table 10.2 below.

Table 10.2: Determinants of delayed diagnosis of HIV status - barriers to HIV testing

Determinants	Deblonde et al. (2010) No. of primary studies (n);
Knowledge, attitudes and beliefs of patients	**Low risk perception (7)** **Fear of HIV disease (8)** **Fear of disclosure (5)**
Knowledge, attitudes and beliefs of health professionals	**Midwife attitudes to value of HIV testing (2) – see discussion section 10.9** **GP anxiety/reticence (3)** **Lack of communication/ advice/ information provided by health professionals (2)**
System	**Accessibility of services (4)** **Lack of knowledge of guidelines in Hungarian prison services (1)** **Resource constraints in Hungarian drug treatment settings (1)** **Resource constraints for targeting African communities in the UK (1)** **Legal consequences deter sex workers and drug users from accessing healthcare in Russia (2)** **Resource constraints in Russia (2)**

Determinants of delay/ Barriers to HIV testing: Key Findings

Knowledge, attitudes and beliefs of patients

- *Low risk perception*: Four studies conducted in the UK, one among a large ethnically diverse HIV-infected clinic population in South London (Boyd et al. 2005), one surveying key informants working in the field of HIV and African communities in Britain (Burns et al. 2007), one surveying newly diagnosed HIV-positive Africans attending HIV treatment centres across London (Burns et al. 2008) and another surveying pregnant women who did not accept an HIV test in an antenatal clinic in London (Campbell et al. 2003), all found that low risk perception was a major influence in the uptake of HIV testing. In a survey among MSM in a STI clinic in Amsterdam (Stolte et al. 2007) and a study among high-risk attendees of two genitourinary medicine clinics in London (Forsyth et al. 2008), low risk perception was the most important reason for declining an HIV test. In a large-scale internet-based survey among Dutch test-naive MSM, low-risk perception was considered an important reason for not taking an HIV test even though 56% reported risky sexual behaviour (Mikolajczak et al. 2006).

- *Fear of HIV disease*: Two studies examining the attitudes of Scottish MSM found fear was an important barrier to HIV testing (Flowers et al. 2003, Knussen et al. 2004). An internet-based survey among at-risk Dutch MSM indicated that fear of a positive test result was the most important obstacle to undertaking a HIV test (Mikolajczak et al. 2006). Fear and not wanting to know or not feeling ready to cope with a positive result were also frequently cited reasons for not accepting an HIV test in a cross-sectional survey among MSM in an STI clinic in Amsterdam (Stolte et al. 2007), as well as in a study among high-risk patients at a genitourinary clinic in London (Forsyth et al. 2008). Two studies examining patients at STI clinics in the Netherlands found that groups at high risk for HIV, especially MSM, declined HIV testing, with fear being the major reason for opting out (Heijman et al. 2009, Dukers et al. 2009). Being afraid was identified as a significant factor in refraining from earlier testing in the survey among newly diagnosed Africans in London (Burns et al. 2008). A survey among sexually active youth in the Balkans found that the most frequently mentioned reason for not having sought an HIV test was fear of diagnosis (Delva et al. 2008).

- *Fear of disclosure*: Black Africans testing for HIV at a London hospital were found to be twice as likely as non-Black UK residents to be worried about future discrimination if they tested positive(Erwin et al. 2002). Another study found that African migrants were fearful of meeting people they knew while undertaking testing as they anticipated blame and future discrimination (Burns et al. 2008). Fear of disclosure increased when accessing community-based services (Prost et al. 2007) and specialist services located in sexual health clinics (Burns et al. 2007, Erwin et al. 2002). Three studies found that participants were fearful that a positive diagnosis might adversely affect the immigration process (Burns et al. 2007, Burns et al. 2008, Erwin et al. 2002). In a survey of Balkan patients, fear of breach of confidentiality was the second most frequently identified barrier to HIV testing among sexually active, untested youth (Delva et al. 2008).

Knowledge, attitudes and beliefs of health professionals

- *Midwife attitudes to value of HIV testing*: These studies pre-date the introduction of universal offer of an HIV test as part of routine antenatal care (see discussion section 10.9 below). One study found that midwife doubt about whether testing was beneficial for all women and whether testing should be promoted, was associated with lower uptake rates (Boyd et al. 1999). Another study concluded that the uptake of an HIV test depends more on the attitude of the individual midwife than the method of offering the test or the time spent on pre-test counselling (Simpson et al. 1998).

- *GP anxiety and reticence*: A survey among GPs in the UK revealed that raising HIV testing in primary care was associated with a high level of

anxiety - the majority of GPs avoided discussing HIV testing with patients, even in high-risk groups (Kellock and Rogstad 1998). Key informants in the field of HIV working with African communities reported that clinicians outside sexual health clinics/ antenatal settings were perceived to be failing to address HIV with their patients, preferring to recommend attendance at a sexual health clinic than to offer an HIV test themselves and thus delaying diagnosis (Burns et al. 2007). A survey of newly-diagnosed HIV-positive Africans attending treatment centres across London found that the subject of HIV testing was not broached by the GP for 82.4% of Africans who subsequently tested HIV positive (Burns et al. 2008).

- *Lack of communication/ advice/ information provided by health professionals*: A multicentre prospective study in maternity units in London showed that in more than one fifth of booking interviews no pre-test discussion about HIV transmission had taken place despite the fact that pre-test discussion increased uptake of testing (Gibb et al. 1998). In a survey of newly-diagnosed HIV-positive Africans attending treatment centres across London which found that HIV testing was not broached by the GP for 82.4% of Africans who subsequently tested HIV positive, 59% believed they would have tested earlier if someone had told them they were at risk of HIV, and advice from a doctor was the principal reason for having an HIV test for 40% of respondents (Burns et al. 2008).

System

- *Accessibility of health services*: One UK study reported that HIV-positive patients attending an HIV outpatient clinic in South London and Black Africans in London were concerned about where to obtain an HIV test and about entitlement to medical care due to immigration status (Erwin et al. 2002). This finding was replicated in another UK survey of key informants working in the field of HIV and African communities and newly diagnosed HIV-positive Africans in London (Burns et al. 2008). A UK survey showed that African migrants were frequently unaware that an HIV test can be obtained at sexual health clinics without the need of referral and that those unfamiliar with health services or with poor knowledge of English viewed appointment systems as intimidating (Burns et al. 2007). Uncertainty about where HIV tests could be obtained was identified as a barrier to testing among sexually active youth in the Balkans (Delva et al. 2008).

- *Resource constraints for targeting African communities in the UK*: Key informants in the field of HIV and working with African communities in the UK noted that political will, advocacy, as well as financial and human resources, are often lacking in order to target African communities in the UK (Burns et al. 2007).

Demographic determinants among Hispanic Americans

Among Hispanics, being foreign-born or male increased the risk for delayed diagnosis (Espinoza et al. 2008, Espinoza et al. 2009). Espinoza et al. (2008) reported 2005 CDC data showing that approximately 40% of Hispanics born in the US had a delayed diagnosis compared to 55% of Mexicans and 59% of Central Americans (AOR 2.2 and 2.5, respectively). The CDC data on heterosexually-acquired HIV infection showed that Hispanic males had a 1.6 (95% CI 1.4-1.8) increased odds of concurrent HIV/AIDS diagnosis compared to Hispanic females (Espinoza et al. 2007).

Along the US-Mexico border, 46% of all Hispanics are diagnosed late compared to 37% of Whites, 51% foreign-born Hispanics have late diagnoses compared to 39% of US-born individuals (Espinoza et al. 2009). In addition, Espinoza et al. (2009) also reported an increased risk of delayed diagnosis among foreign-born males (AOR 1.7, 95% CI 1.4-2.2) compared to US-born males, but not between foreign-born and US-born females. Three studies evaluated the difference between foreign-born and US-born individuals with respect to delayed enrolment in HIV care (Kelly et al. 2007, Levy et al. 2007, Wohl et al. 2009). Foreign-born Hispanic males were at particularly high risk for late presentation to care (Kelly et al. 2007). Levy et al. (2007) found that Hispanics were not at greater risk of late presentation when compared to non-Hispanics, but immigrants (79% Hispanic) were almost three times more likely to have an opportunistic infection (OI) at HIV diagnosis than non-immigrants (7% Hispanic).

Adjusted analysis showed no difference by place of birth or gender, although Spanish-speaking Hispanics were almost three times more likely to present late compared to English- speaking Hispanics (Wohl et al. 2009).

10.5 Outcomes

None of the studies within the included review examined the outcomes of delayed diagnosis of HIV positive status.

10.6 Cost Implications

None of the studies within this review examined the cost implications of delayed diagnosis of HIV positive status.

10.7 Interventions

No interventions were described or evaluated within the included systematic review.

10.8 Types of delay

None of the studies within the included review estimated the average time intervals for any particular stage of the diagnostic process.

10.8.1 Patient delay

Low risk perception, fear of a positive diagnosis and fear of disclosure were all identified as barriers to HIV testing. Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk

behaviours were more likely to avoid testing as a result of fear of a positive diagnosis. Fear of disclosure was a particular concern among African communities in the UK. Uptake of testing was inhibited among migrants who thought that HIV status might have a bearing on the immigration process.

10.8.2 Doctor delay
GPs were reluctant to discuss HIV testing with patients, even in high-risk groups, preferring instead to refer patients elsewhere, thus delaying diagnosis. GPs failed to adequately communicate the value of HIV testing to patients.

10.8.3 System delay
Confusion and concern about where to obtain an HIV test and about entitlement to medical care due to immigration status was reported among HIV-positive Black Africans in London. Key informants in the field of HIV and working with African communities in the UK noted resource constraints for targeting HIV testing services.

10.9 Discussion

The findings of the review conducted by Chen et al. (2011) have limited relevance to the UK, focussing as they do, upon Hispanic Americans. However, within this group foreign-born individuals or males had an increased risk for delayed diagnosis and Spanish-speaking Hispanics were almost three times more likely to present late compared to English-speaking Hispanics. Given that the focus of both the included systematic reviews was upon the determinants of delay, it was unsurprising that evidence regarding the prevalence, outcomes, cost implications and interventions to reduce delayed diagnosis were absent.

With respect to the determinants of delayed diagnosis of HIV infection, the majority of evidence focussed upon the influence of the knowledge, attitudes and beliefs of patients upon the uptake of testing. Low risk perception, fear of a positive diagnosis and fear of disclosure were all identified as barriers to HIV testing. Those declining HIV tests often perceived themselves to be at low-risk of infection. However, the finding that those engaging in high-risk behaviours were more likely to avoid testing as a result of fear of a positive diagnosis, was of particular concern given the implications in terms of onward transmission.

Fear of disclosure was a particular concern among African communities in the UK. Confusion and concern about where to obtain an HIV test and about entitlement to medical care due to immigration status was reported among HIV-positive Black Africans in London. Key informants in the field of HIV and working with African communities in the UK noted resource constraints for targeting HIV testing services.

The finding that GPs were reluctant to discuss HIV testing with patients (even in high-risk groups) and preferred instead to refer patients elsewhere, implies that delays are occurring, in the best case scenario, due to onward referral.

Although we failed to find any information regarding the prevalence of delayed diagnosis of HIV infection, data from the Health Protection Agency suggests that

late diagnosis of HIV is substantial: of the 6,658 new HIV diagnoses made in 2010, 50% were late (with a CD4 cell count of <350/mm^3) and 28% very late (with a CD4 count <200 cells/mm^3) (Health Protection Agency, 2011).

None of the primary studies within the included reviews examined the outcomes of late diagnosis of HIV. However, a late (CD4 count <350/mm^3) or very late (CD4<200/mm^3) HIV diagnosis is associated with increased morbidity and mortality: a quarter of deaths among HIV positive individuals in the UK are among those diagnosed too late for effective treatment, and individuals starting antiretroviral therapy with a CD4 count below 350 cells/mm^3 have a significantly increased risk of contracting opportunistic diseases (Health Protection Agency, 2011). Furthermore, undiagnosed individuals have been estimated to have a rate of onward transmission three times higher than those who are diagnosed with HIV infection, and be more than twice as likely to have unprotected sex (Marks et al. 2006).

Again, the included systematic reviews did not provide any data relating to the cost implications of delayed diagnosis of HIV infection. However, recent UK primary research has demonstrated that the annual treatment cost for HIV infected individuals decreased as CD4 count increased, with the biggest differences observed between starting highly active anti-retroviral treatment regimens (HAART) with a CD4 count ≤200 cells/mm^3 compared with a CD4 count >200 cells/mm^3 (Beck et al 2011a). Beck and colleagues concluded that while starting patients on a first-line HAART regimen at CD4 counts ≤350 cell/mm^3 would increase the number of patients receiving HAART and initially increase the population costs of providing HIV services, earlier treatment on cost-effective regimens would maintain patients in better health and result in reduced use of health and social services (thereby generating fewer treatment and care costs and enabling people living with HIV to remain socially and economically active members of society). Nevertheless, Beck et al. (2011b) note that 25% of HIV positive individuals accessing services continue to present with a CD4 count ≤200 cells/mm3, which highlights the need to investigate the cost-effectiveness of testing and early treatment programs for key populations in the UK.

The National Institute for Health and Clinical Excellence has produced a costing model which estimates that a shift of 1% of patients being diagnosed at an earlier stage of disease effects a reduction in treatment costs and creates savings: approximately £212,000 a year for men who have sex with men and £265,000 a year for black Africans in England. The cumulative effect of onward transmissions avoided means that over time savings would increase and become greater (NICE, 2011).

There were no primary studies within the included reviews examine interventions to reduce delayed diagnosis of HIV infection. However, eight Department of Health funded projects conducted in high prevalence areas in the UK between 2009 and 2010 resulted in more than 10000 HIV tests being performed and appeared to be effective in detecting new cases: together they generated a total of 50 newly diagnosed individuals giving an overall positivity of five per 1000 tests. The

estimated annual cost of expanding testing into general medical services nationally in areas of high prevalence with coverage of 75% would be £1.3 million: the cost for an average high prevalence PCT would be £19,000 per 100,000 people (Health Protection Agency, 2010).

Finally two primary studies within Deblonde et al. (2010) focussed upon Midwife attitudes to the value of HIV testing. It must be noted however, that these studies pre-date universal offer of an HIV test as part of routine antenatal care. Since its introduction in 1999, uptake of HIV testing among women in antenatal care has reached 95% nationally, the proportion of women who remain undiagnosed after delivery fell from 27% in 2000 to 12% in 2009 and the estimated proportion of newborns at risk of HIV infection who become infected fell from 8% to 2% between 2000 and 2008 (Health Protection Agency, 2010).

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11. Myocardial Infarction

Coronary heart disease is one of the most common causes of morbidity and mortality in the UK (Department of Health 2000), with the risk of mortality greatly increased during acute myocardial infarction. Research and practice over the last decade has shown much improvement on the rates of survival, and reduced morbidity when patients are treated with primary angioplasty rather than thrombolytic drugs (Terkelsen et al. 2007, Boersma et al. 2006).

The systematic reviews in this chapter review evidence that is, in some cases, over ten years old and, although helpful in supporting service change at the turn of the century, it is regarded as out of date by clinical leaders as treatment and practice has moved on considerably.

Therefore we will use the reviews to introduce information in the discussion section about more recent research and service change in this area of medicine for the UK. The primary research is not part of a systematic assessment exercise.

There are two types of myocardial infarction, namely ST elevation myocardial infarction (STEMI) where there is a complete blockage of an artery in the heart, and nSTEMI were the artery is partially blocked. We will discuss mainly STEMI, as this requires an emergency reperfusion treatment and where time delay impacts on outcomes such as mortality, recurrence of the myocardial infarction and an increased possibility of stroke.

11.1 Overall summary of findings

Much of the information in the reviews is out of date as medical practice in this field has moved on since they were published.

Patient delay is the most difficult area to tackle and evidence from public awareness campaigns is weak, suggesting that the increase in the use of emergency services is not offset by gains in earlier diagnosis.

Pre-hospital ECG, administered by paramedics, decreases the time to treatment.

Primary percutaneous coronary intervention is the treatment of choice despite the need to transfer some patients to a specialist centre.

There is no information on prevalence, outcomes or costs in the reviews.

11.2 Included Studies

We found six systematic reviews that examined STEMI (Brainard et al. 2005, Hewitt et al. 2004, Dubayova et al. 2010, Morrison et al. 2006, Boersma et al. 2006, De Luca et al. 2008). Both Brainard et al. (2005) and Morrison et al. (2006) reported on

the impact of pre-hospital ECG on the reduction of time to treatment, and therefore there was considerable overlap in the small number of studies they found. Hewitt et al. (2004) and Dubayova et al. (2002) investigated determinants of patient delay, with Hewitt and colleagues additionally covering interventions to reduce delay. Boersma et al. (2006) compared outcomes for patients receiving primary percutaneous coronary intervention (PPCI) and in-hospital fibrinolysis (FL), and De Luca et al. (2008) assessed the impact of transfer delays to tertiary centres with catheter labs to carry out the mechanical reperfusion of PPCI.

The characteristics of the reviews are presented in table 11.1.

Number of Contributing Reviews: 6

Table 11.1: Characteristics of the Included Reviews

Systematic Review [AMSTAR score]	No. of included studies	Pooled number of participants	Countries	Participants	Disease state / Condition
Boersma et al. 2006 [10/11]*	22 trials	6763 patients, 3383 randomised to FL and 3380 to PPCI	Not reported	Age: median (range) FL - 62 (53-71) PPCI - 63 (52-68) Male (%) FL - 73.2 PPCI - 72.6 Diabetes mellitus (%) FL - 12.4 PPCI - 13.5 Previous MI (%) FL - 13.2 PPCI - 12.5	Not reported
Brainard et al. 2005 [9/11]	4	99	USA	People with a suspected heart attack.	Not reported
De Luca et al. 2008 [10/11]*	11 trials	5741 patients 2974 PPCI, 2767 thrombolysis	Not reported	Age: Mean >55 Gender Majority male	Not reported
Dubayova et al. 2010 [11/11]*	15 studies of which 4 focused on AMI	1634	North America Australia Germany USA	Adults	Not reported
Hewitt et al. 2004	11 predictor studies	Predictor studies -	USA (10), UK (2),	Gender: mixed	Not reported

[11/11]*	11 intervention studies	12,207 Intervention studies – 76,502 (one study did not state no. of participants)	Sweden (2), Germany (2), Netherlands, France, Italy, Canada, Australia, Switzerland	Ethnicity: mixed Age: majority >44 years	
Morrison et al. 2006 [9/11]*	5	Not reported	Not reported	Patients with suspected myocardial infarction	Not reported
Those studies marked with an asterix satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool.					

Three of the four studies in Brainard et al. (2005) were also used in Morrison et al. (2006).

11.3 Prevalence

There was no information about prevalence in these reviews.

11.4 Determinants

There was no overlap between Hewitt et al. (2004) and Dubayova et al. (2010), however, they both examined patient delay and the factors that contribute to help seeking behaviour. These factors are described in table 11.2, with the number of primary papers contributing to each, and whether the determinant led to a longer delay (+) or a shorter delay (-) or no (□) association in seeking help. Associations with risk of delayed referral are statistically significant unless indicated non-significant (NS).

Table 11.2: Determinants of Delay in Help Seeking

Determinant	Hewitt et al. (2004)	Dubayova et al. (2010)
Demographic	Gender (4□) Female (3+, (1?NS)) Male (1-?NS) Age (4□) Older age (1+) >65 years (1+) Ethnicity (3□) SES Income source (1□) Employed (1+) Lower socioeconomic status (1+?NS)	

Determinant	Hewitt et al. (2004)	Dubayova et al. (2010)
	Education level (1□) High professional group (1-?NS) Married (1-, 1□)	
Medical	Co-morbidities Diabetes (1□) Hypertension (1□) Disease status (chronic or not) (1□) Smoking Status Ex or current smoker (1-?NS, 1□) Previous diagnosis (1□) Subsequent confirmation of ischaemic heart disease (1□) Acute AMI (1+) Pulmonary oedema (1-) History of ischaemic heart disease (1□) No previous CCU care (1+?NS) Previous AMI (1-) Previous pulmonary oedema (1+) Level of pain Severe pain (2-) Less pain (1+?NS) Pain in 24 hours prior to inclusion (1+) but if pain still present (1□) Breathlessness (2-NS) Greater no. of symptoms (1-?NS) Continuous symptom pattern and increase in intensity (1-)	
System	Access Insurance status (1+, 1□) Public hospitals (v. private) (1+) Geographical location (1□) Difficulty in access (1□) Consulting with medical professional while experiencing AMI (1+) Recent consultation with	

Determinant	Hewitt et al. (2004)	Dubayova et al. (2010)
	doctor (1+?NS) Calling the correct agency (1+?NS)	
Patients' knowledge, attitudes and beliefs	More comfort in seeking medical help (1-) Perceived inability to control symptoms (1-) Those who sought care for 6 symptoms (swelling of ankles, chronic fatigue, shortness of breath, fainting spells, chest pain, persistent cough) (1-) Psychological activity before onset (1-) High degree of anxiety (1-) Active problem solvers (1-NS) Those who sought more social support (1-NS) Those who had more easing thoughts (1-) Those who were less likely to deny feelings of resentment (1-) Those who were less likely to deny vital exhaustion (1-NS) High degree of impatience (1+) Lower levels of anxiety (1+?NS) Anxiety and delay time (1□) Not believing they were suffering an MI (1+?NS) Symptoms attributed to the heart (1-) Greater perception of seriousness of symptoms (1-)	Worried about troubling others for assistance (2+) Feared consequences of seeking help (2+) (financial fears in USA but not Australia) 'Having fear' (1+) Less anxiety (1+) Evaluation of symptoms as life threatening and causing a feeling of panic or death anxiety (1-) Fear of immediate hospitalization (1-)
Other	Symptom onset at home (2+) Symptom onset not at work or at home (1-) Less than 4 people present (1+?NS) Patient called for help (1-)	

Determinant	Hewitt et al. (2004)	Dubayova et al. (2010)
	Presence of another person (1-) Patient initiative to call for help (1-) Patient intention to turn over the situation to lay others (1-) Lay other did not usurp control of the situation (1+) Lay secondary advice to seek physician consultation (1+) Attempts at self treatment (1□) Attempts to relieve pain by resting (1+?NS) Ingesting heart medication (1-?NS)	

Key Findings

Hewitt et al. (2004) commented that the predictor studies were of poor quality, so their findings should be viewed with caution.

Demographic

- There is some evidence to suggest that women and possibly older people delay longer in seeking help. Lower socio economic status and having a job may also mean delay, but high professional status and being married may be protective factors.

Medical

- There were no significant associations between co-morbidities such as diabetes, hypertension or chronic disease, such as angina, and patient delay. Current and ex-smokers were more ready to call the emergency services.
- Previous experience of AMI and cardiac care in hospital predicted shorter delays, however no significant associations were found for shorter delays for people with a history of ischaemic heart disease, a previous diagnosis of a heart condition, or a subsequent confirmation of ischaemic heart disease.
- High levels of pain predicted shorter delays, as did a greater number of symptoms. If pain was intermittent, delays were longer, but shorter if the pain was continuous and rising in intensity. Breathlessness may also prompt help seeking.

System

- Longer delays were experienced by patients consulting a physician rather than the emergency services, while they were suffering an AMI.

Patients' Knowledge, Beliefs and Attitudes

- Patients who experienced greater anxiety and felt more comfortable about seeking medical help were more likely to contact the emergency services earlier. Those with shorter delays may be active problem solvers, be more ready to seek social support and think more about easing their pain.
- Shorter delays were associated with identification by the patients of the seriousness of their symptoms and attribution of them to the heart. By contrast, those who did not believe they were suffering a heart attack or who experienced only mild anxiety, were less likely to seek help quickly.

Other

- There was mixed evidence about the protective factors of having other people present when someone was experiencing a heart attack. Delays occurred if onset happened in the home or at work, but not if in other public places. One study suggested that if there were less than four people present, there could be longer delays, but another found that having another person present was protective.
- If the patient took the initiative to call for help, delays were shorter, but a readiness to give control of the situation to a lay other who was willing to take on the responsibility, meant quicker access to care. If the lay other decided to consult a doctor rather than call for an ambulance, delay was longer.
- Attempts to alleviate the pain by resting may result in longer delays, but taking heart medication suggested a shorter delay.

11.5 Outcomes

There was no information about the outcomes of late diagnosis of STEMI.

11.6 Cost Implications

There was no information about the cost implications of late diagnosis and heart conditions.

11.7 Interventions

Hewitt and colleagues reported on a mass media and public educational interventions directed at the general public and health professionals to improve recognition of symptoms and knowledge about appropriate action. Two reviews (Brainard et al. 2005, Morrison et al. 2006) investigated the impact of pre-hospital 12 lead electrocardiogram (ECG) on time to treatment, and as there was an overlap of three studies, the combined reviews included five studies. Boersma et al. (2006) analysed the outcomes from trials testing the relative merits of fibrinolysis

compared with primary percutaneous coronary intervention (PPCI), and De Luca et al. (2008) examined the impact on outcomes for patients who were transferred to a specialist hospital to receive PPCI as opposed to being treated with thrombolytic drugs at hospital.

In Hewitt et al. (2004), eleven studies evaluating mass media and public education interventions to reduce delay were included in the review (one study also examined one to one education). There were two RCTs, one controlled study and eight before and after studies. The key factors covered by the campaigns were: importance of quick / immediate action; emphasis on the signs and symptoms of AMI; importance of calling the emergency services; emphasis of treatment such as lysis; and the use of a specific slogan.

The studies examined a variety of outcomes, including pre-hospital or patient delay, use of emergency services, rate of treatment and mortality. The results of the outcomes are presented in table 11.3. Two studies reported on the costs of their media campaigns: Call Fast, Call 911 (Meischke et al 1997) – US $245,250 for a mass media campaign, not including costs of a mailing campaign; REACT (Luepker et al 2000) – for town with 100,000 residents, the annual cost was between US$156,000 and US$294,000 (the variation in costs is due to differences between cities in labour, rent, media and distribution costs).

In summary, five studies reported statistically significant positive findings, but four of these were before and after studies, and one was a controlled study. Of the six studies showing no difference, two were RCTs and four were before and after studies. The increased use of emergency services from public awareness campaigns has to be of concern as it places extra burdens on the health service and does not seem to result in significant gains to early diagnosis. Hewitt and colleagues concluded that the evidence was limited for these campaigns because the weakness of the before and after study design meant it was impossible to determine if the effects were from the intervention or other factors occurring at the same time as the intervention.

For pre hospital ECG, Morrison and colleagues looked at three different outcomes: the pre-hospital on scene time; the door-to-needle interval; and all cause mortality. They found that on scene time was not significantly different with pre-hospital ECG for 519 cases (pooled weighted mean difference of 1.19 minutes [95% CI =-0.84 to 3.21]). In 181 cases, the door-to-needle interval decreased with the use of ECG and advance hospital notification (weighted mean difference of 36.1 minutes [95% CI = -63.0 to -9.27]. They found significant heterogeneity among the studies which weakened the conclusions that could be drawn from the pooled results (Q statistic = 10.9, p < 0.01). One study reported on mortality and found no statistical difference in all-cause mortality in patients with advance hospital notification as compared to standard management (15.6% in the concurrent control group versus 8.4% in the intervention group, p = 0.22).

Brainard and colleagues reported on a smaller sample size, namely 54 patients with a pre-hospital ECG and 45 without, and presented results in terms of mean average unweighted time to reperfusion. They found a difference of 24.7 (95% CI, 16.7 -

32.7) minutes in time to reperfusion therapy between treatment and control groups.

Table 11.3: Results from the Intervention Studies in Hewitt et al (2004)

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Meischke 1997 (USA, RCT)	∫ (=) No significant differences between intervention groups and control			∫ (↑) A significant increase in no. of visits to ED for chest pain. Remained higher for 3 months after campaign but not statistically significantly so.	∫ (↑) A significant increase in the no. of calls. The number of 911 calls. Remained statistically significantly higher for 3 months after campaign.		∫(↑) A significant increase in the number of CCU admissions with admitting diagnosis of rule-out MI. Remained higher for 3 months after campaign but not statistically significantly so.	
Luepker 2000 (USA, RCT)	∫ (=) Delays declined in both groups, but not significantly between intervention and control. Delay trend in intervention group = -4.7% per year (95% CI: -8.6%, -0.6%) Delay trend in control group = -6.8 % per year (95% CI: -14.5%, 1.6%)		∫ (↑) 20% increase for intervention group (OR 1.20 95% CI: 1.07, 1.34)	∫(=) Visits declined for both groups			∫(=) Admissions increased for both groups but not significantly different	∫(=) Case fatality rates decreased from 2.66% at baseline to 1.78% at trial end in the control and from 3.23% to 2.43% in the intervention group. However this decrease was not statistically significant for either group. In terms of survival, there was no difference between intervention and control hospital death rates.

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Rowley 1992 (UK, controlled trial)		∫(↓) For patients with definite and probable infarction in intervention practices, 22% called for help within 30 minutes before intervention and 44% during (p<0.05), and 24% before and 23% during for control practices.	∫ (=) No. of people calling GP declined for both groups					

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Mitic 1984 (Canada, before and after study)	∫ (↓) An increase in the % of persons exhibiting pre-hospital delay of < / = two hours from before (15.8%) to during (31.3%) the eight weeks of intervention (p<0.05). This was not maintained after the intervention.							
Ho 1989 (USA, before and after study)		∫(=) No differences found in % of patients exhibiting patient delay within certain time frames				∫ (=) No differences found		
Moses 1991 (USA, before and after study)	∫ (=) No statistical analysis but little difference shown			∫ (=) No differences found				

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Rustige 1992 (Germany, before and after study)	√ (=) Showed a decrease in delay at first but this was not maintained							
Bett 1993 (Australia, before and after study)		√ (=) No change. Median patient delay one month before the intervention took place = 1 hour. During the second month after intervention had stopped = 1 hour						

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Blohm 1994 (Sweden, before and after study)	ʃ (↓) A decrease in median pre-hospital delay from 3 hours before the intervention to 2 hours and 20 minutes during the 14 months of the intervention (P<0.001)			ʃ (↑) An increase in the mean number of persons with chest pain per day in the ED from before (n=10) to the first week during (n=25) intervention (p<0.001), and from before to first month during (n=19) the intervention (p<0.001). This was not maintained during first year		ʃ (=) No differences found		ʃ (=) One-year mortality rate among patients with AMI was reported to be the same for before, during and after the intervention (25%). In-hospital mortality among patients with AMI did not change during (13%) compared to before (14%) the intervention.
Gaspoz 1996 (Switzerland, before and after study)	ʃ (↓) A decrease in median pre-hospital delay from before to during the 12 months of campaign by twenty five minutes (p<0.001)	ʃ (↓) A decrease in median patient delay from before (86.5 minutes) campaign to during (60 minutes) the 12 months of campaign (p<0.001)		ʃ (↑) An increase in the mean number of visits to the ED for chest pain per week before (n=22.2) and during the first week (n=49) of the campaign (p<0.01). This increase remained statistically significant for the first six (p<0.005) and 12 months (p<0.005) of intervention. Increase in ED visits for chest pain during the first week was result of a more than twofold	ʃ (↑) An increase from before (13%) to during (20%) the 12 months of the intervention (p<0.001).	ʃ (=) No differences found		

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
				increase in visits for AMI and unstable angina (p<0.01) and visits for chest pain of non-cardiac origin (p<0.05). At six (p<0.02) and 12 months (p<0.02) the increase in ED visits per week for AMI and unstable angina was still statistically significant, whereas it was not statistically significant for visits owing to non-cardiac chest pain.				

Study (Country, design)	Pre Hospital Delay	Patient Delay	Use of emergency services					Mortality
			Use of emergency services	No. of ED visits	No. of calls to emergency switchboard	Use of ambulance	Hospital admission	
Maeso-Madronero 2000 (Germany, before and after study)	∫ (↓) 1.a statistically significant decrease in median pre-hospital delay from before (4 hours) to during (2.9 hours) the six months of the campaign (p=0.007). 2. a statistically significant increase in the % of patients admitted within 1 hour and within 6 hours from before (15.5% and 58.5 %, respectively) to during (23.2% and 66.0%, respectively) the six months of intervention (p=0.01 and p=0.05, respectively)							

∫ = outcome measured; (↑) = an increase for the intervention group, may not have statistical analysis but detail given where possible; (↓) = a decrease for the intervention group, may not have statistical analysis but detail given where possible; (=) = no statistically significant difference between intervention and control groups, or between baseline and post intervention.

In recent years, primary angioplasty (PPCI) has become the preferred treatment over the application of clot busting drugs (fibrinolysis) because blood flow is more likely to be restored after PPCI (29-54% vs. 90%) (Grines 1996). However, PPCI requires a catheter laboratory at tertiary hospitals to be available at all times for emergency reperfusion, necessitating a delay for some patients while they are transferred for treatment. By contrast, fibrinolysis can be delivered at most hospitals or by paramedics.

Boersma and colleagues pooled the results of 22 randomised trials where patients had been randomised to either in hospital fibrinolysis (FL) or PPCI, to assess the relationship among treatment, treatment delay and 30 day mortality. They only included trials where individual patient data were available, and their overall sample was 6763. Patients in both groups were balanced, with the exception of those with a coronary artery bypass graft who were more likely to be randomised to the FL group, (p<0.05).

They found that PPCI was more effective than fibrinolysis in relation to mortality after 30 days (7.9% of FL patients vs. 5.3% PPCI patients, p<0.001), and re-infarction during the 30 day follow up (6.4% of FL patients vs. 2.4% of PPCI patients, p<0.001). In both treatment groups there seemed to be a trend of increased death or re-infarction when presentation delay was longer (from less than an hour to over 6 hours), but this was only statistically significant in the FL group (p<0.001). There were fewer incidences of stroke in the PPCI group at 30 days (0.5% vs. 2.2%).

When they looked at treatment delay for PPCI, they discovered that PPCI was associated with a 67% reduction in the odds of 30 day mortality in comparison with FL, if the delay was less than or equal to 35 minutes and with a 28% reduction in patients with a longer PPCI related delay (pBreslow-Day = 0.004 for the comparison of the first quintile with quintiles 2-5 (from >35 minutes to 120 minutes))

The median presentation delay of patients from both groups was similar [FL – 143 (91-225) min and PPCI – 140 (91-220) min, p=0.30]. Younger, male patients and those with a history of heart attacks tended to present earlier and those with diabetes mellitus later, especially after 6 hours. As expected, the median time to FL was significantly shorter than that of the start of PPCI [19 (10-30) min vs. 76 (61-95) min; p<0.001], which gave an overall PPCI related delay of 55 (37-74) min.

De Luca et al. (2008) investigated the issue of relative benefits in terms of survival of transfer for angioplasty over the administration of thrombolysis on site for STEMI patients. This study updated an earlier meta-analysis by Dalby et al. (2003). They included 11 randomised trials with a combined sample of 5741 patients. In two of the trials, CAPTIM (Bonnefoy et al. 2002) and SWEDES (Svensson et al. 2006), thrombolytic drugs were administered in an out of hospital setting by paramedics, and for this reason analyses were conducted that both included and excluded these studies. The individual studies lacked statistical power, but in combining them the authors were able to report significant results.

They found that transfer for PPCI was associated with a significant reduction in mortality (5.6% vs. 6.8%; OR=0.77 [95% CI 0.62 to 0.96] p=0.02 [random-effect model]; NNT=83.3). The benefits were confirmed after the exclusion of the CAPTIM and SWEDES trials and the results were not affected by study quality. After meta-regressions, the survival benefits for transfer were not related to PPCI time delay (r=-0.002; ß=0.00001 [95% CI – 0.008 to 0.008]; p=0.99), but were related to the

baseline mortality risk of the lytic group, suggesting reduced benefit for low risk patients (r=-0.63; β =-3.84 [95% CI -7.39 to 0.29]; p=0.037). This finding did not reach statistical significance when the CAPTIM
and SWEDES studies were excluded and the PPCI related time delay was added as a co-variate to the regression model.

Transfer for PPCI was also associated with a significant reduction in re-infarction at the 30 day follow up (2.1% vs. 4.7%; OR= 0.42 [95% CI 0.31 to 0.57]; p<0.001 [random effect model]; NNT=38.5). This was confirmed after the exclusion of the CAPTIM and SWEDES trials and it was not affected by study quality. There was no significant relationship between the benefits in re-infarction with transfer for angioplasty and the baseline mortality of the lytic group (p=0.83) and PPCI related time delay (p=0.99), and this held after the exclusion of the CAPTIM and SWEDES trials.

Lastly, transfer for primary angioplasty was associated with a significant reduction in occurrence of stroke at 30 days (0.7% vs. 1.7%; OR = 0.41 [95% CI 0.20 to 0.84]; p=0.02 [random effect model]; NNT = 100). Similar results were obtained after the exclusion of the CAPTIM and SWEDES trials and they were not affected by study quality.

11.8 Types of Delay

11.8.1 Patient Delay
This remains the most intractable part of delays in the diagnostic process and there is evidence that mass media campaigns increase the use of emergency services without sufficient gain in earlier diagnosis.

11.8.2 System Delay
The evidence for the increased benefits of PPCI over thrombolysis has meant a shift in how treatment is delivered once the emergency service response is triggered. The delays associated with hospital transfer to a catheter laboratory do not seem to reduce the benefits of PPCI so substantially that thrombolysis should be preferred.

11.9 Discussion

The reviews for heart conditions focused on determinants and interventions to reduce treatment delay. Studies identified that patient delay in seeking help was a key determinant and Hewitt et al. (2004) examined both predictors for this kind of delay and interventions to reduce it. Although they were critical of the papers, they found with Dubayova et al. (2010) that delay is associated, among other factors, with emotions such as fear and anxiety, correct attributions of pain to the heart by patients, and the patient's willingness to be helped either by the medical services or by lay others.

Hewitt and colleagues did not find strong evidence to support mass media campaigns to inform the public about the symptoms of heart attacks, and the action to take if one is suspected. The increased use of emergency services by those who are false positives places extra resource burdens on the NHS. Yet there are people who present late, such as those with diabetes mellitus, who could benefit from more targeted messages from trained volunteers, which is a strategy

adopted by the British Heart Foundation Chest Pain programme. However, patient delay remains the most intractable part of the delays in the diagnostic process.

Both Brainard et al. (2005) and Morrison et al. (2006) found that a pre hospital ECG reduced delay to reperfusion therapy in hospital. Recent UK research by Quinn et al. (forthcoming) on a large dataset of patients from the MINAP (Myocardial Ischaemia National Audit Project) registry found that pre hospital ECG enabled patients to receive treatment within the recommended time ('call to balloon' time ≤ 90 mins (27.88% vs 21.42%, OR 0.73, 95% CI 0.65-0.81) for PPCI, and 'door to needle' time ≤ 30 mins (90.61% vs 83.68%, OR 0.54, 95% CI 0.47-0.62) for those receiving fibrinolytic therapy in hospital). This, in turn, affected mortality, with lower hospital (4.0% vs 4.7%, OR 0.91, 95% CI 0.86-0.95) and 30 day (7.4% vs 8.2%, OR 0.95, 95% CI 0.91-0.99) mortality for STEMI patients who received reperfusion treatment. Pre hospital ECG use increased from 48% to 68% over the period of the study (January 2005 to December 2009), but overall only 50.3% of emergency patients received pre-hospital ECG.

In 2002 few UK centres offered PPCI, but evidence, from trials and observational studies (Huynh et al. 2009), showed that the procedure offered greater benefits in terms of survival and complications than thrombolysis treatment. Professor Boyle, then National Director for Heart Disease and Stroke, set out the case for developing these services (Boyle and Department of Health 2006), and the National Infarct Angioplasty Project (NIAP) was established to collect and analyse data from seven PPCI pilots from April 2005 to March 2006. In 2008, they concluded their study and reported that PPCI could be delivered within acceptable treatment times. Of those patients admitted directly to a catheter laboratory in a PPCI centre, 98% achieved a 'door to balloon' (DTB) time of less than 90 minutes (NIAP 2008).

Since 1999, MINAP has collected clinical audit data from a network of hospitals on the care of patients with heart attack. In its most recent statement, it reported an increase of centres offering PPCI over the last 10 years from 86 in England and 2 in Wales to 133 and 8 respectively. Table 11.4 shows the increase of patients treated with PPCI within the recommended times, and the relative decrease in thrombolytic treatment in hospitals, (Belfast hospitals do not report use of any thrombolytic treatment). For PPCI, a greater percentage of patients were treated within the recommended time, i.e. 150 minutes from calling for professional help, if they were taken directly to a heart attack centre – 88% in England, 76% in Wales, 89% in Belfast (MINAP 2011).

Since the publication of the National Service Framework for Coronary Heart Disease in 2000 (Dept of Health 2000), coronary medicine has changed considerably, and so much of the information from the earlier studies examined in the reviews is out of date. NICE has produced guidelines for the management of nSTEMI (National Clinical Guidelines Centre 2009) and guidelines for STEMI will be published soon, based on more recent primary studies. Data from a recent study looking at delays to reperfusion across four regions of the world show that Europe (including data from the UK) has the shortest times to PPCI and fibrinolysis (Spencer et al. 2010).

Table 11.4: Percentage of patients treated within the recommended timeframe (MINAP 2011)

Year	Door to balloon time: % of patients treated within 90 mins of arrival at hospital			Call to balloon time: % of patients treated within 150 mins of calling for help			Door to needle time: % of patients treated within 30 mins of arrival at hospital			Call to needle time: % of patients treated within 60 mins of calling for help		
	England	Wales	Belfast	England	Wales	Belfast	England	Wales	Belfast	England	Wales	Belfast
2010/11	90%	68%	87%	81%	75%	90%	75%	62%	-	68%	53%	-
2009/10	89%	71%	53%	80%	76%	77%	79%	67%	-	69%	55%	-

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12. Psychosis

Duration of untreated psychosis (DUP) may be defined as the interval from manifestation of first psychotic symptom to initiation of adequate treatment (Marshall et al. 2005). Long DUP is common, may be associated with poor outcomes and as such, strategies to enhance early detection of first-episode psychosis (FEP) have been advocated (Lloyd-Evans et al. 2010). Early intervention services (EIS) for psychosis are intended to detect emergent symptoms, reduce DUP and improve access to effective treatments (Bird et al. 2010). Early intervention has been adopted as a therapeutic approach in America, Europe and Australasia (Marshall and Rathbone 2011).

12.1 Overall summary of findings

The duration of untreated psychosis, i.e. the time interval between symptom initiation and diagnosis and/or treatment, was found to have a median of 21.6 weeks, with a range of four to 68 weeks.

Longer duration of untreated psychosis (DUP) is associated with greater severity of positive symptoms after treatment, greater severity of global symptoms after treatment, poorer social functioning, more likely relapse and lower rates of remission.

We found no information about cost implications in the included reviews.

The results of studies reporting on the impact of multi-focus awareness campaigns on reducing DUP were mixed and conflicting.

Specialised teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, larger trials are needed to confirm this.

Results from small scale trials, which have not been replicated, suggest that E-EPA oil, the anti-psychotic amisulpride, and a combination of anti-psychotics and CBT are strategies that warrant further investigation for the prevention of transition to psychosis.

12.2 Included studies

We found seven systematic reviews relating to delayed diagnosis for psychosis (Anderson et al. 2010, Bird et al. 2010, Farooq et al. 2009, Lloyd-Evans et al. 2010, Marshall et al. 2006, Marshall and Rathbone 2011, Perkins et al. 2005).

Anderson et al. (2010) examined the nature and determinants of the pathway to care of patients experiencing a first psychotic episode.

Marshall et al. (2005) carried out meta-analyses of correlational data and of data derived from comparisons of long and short DUP groups to examine the association between DUP and outcome in cohorts of first-episode patients. Perkins et al. (2005) also conducted a meta-analysis examining the relationship between duration of untreated psychosis and treatment outcomes. Farooq et al. (2009) undertook a meta-analysis to examine the relationship between DUP and outcomes in low-and-middle-income countries.

Lloyd-Evans et al. (2010) examined the effectiveness of early detection initiatives to reduce DUP.

Marshall and Rathbone (2011) evaluated the effects of early detection, phase-specific treatments and specialised early intervention teams in the treatment of people with prodromal symptoms or first episode psychosis (FEP). Bird et al. (2010) also evaluated the effectiveness of early intervention services (EIS), in addition to cognitive-behavioural therapy (CBT) and family intervention in early psychosis.

Where reviews have provided summary measures of DUP i.e. the time interval between symptom initiation and diagnosis and/or treatment, findings of this kind are presented in the section on prevalence below.

The characteristics of the seven included reviews are presented in Table 12.1 below.

Number of contributing reviews: 7

Table 12.1: Characteristics of the systematic reviews investigating delayed diagnosis in psychosis

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Anderson et al. (2010) [7/11]	30: 21 examined pathways to care; 9 examined determinants of pathways; 15 examined impact of pathway to care on DUP.	3563	UK (7) Canada (6) Germany (2) Malaysia (2) USA (2) Singapore (2) Australia (1) China (1) France (1) Iran (1) Ireland (1) Japan (1) NZ (1) South Africa (1) Switzerland (1) Trinidad (1)	Patients with first episode psychosis (FEP). % Male: mean 67.2%, range (40-80%).	*Psychosis* Not defined. *DUP* Not defined.
Bird et al. 2010 [8/11]*	11	1708	Not reported.	Participants recruited from community mental health teams and in-patient and out-patient services. Patients making contact for first or second time, duration since first psychotic episode < 5yrs.	*Early Psychosis* Early psychosis defined as clinical diagnosis of psychosis within 5 yrs of first psychotic episode or presentation to mental health services. Interventions addressing high-risk groups or prodromal populations were excluded.

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Farooq et al. 2009 [8/11]*	11	1538	China (2) India (2) Turkey (2) Mexico (1) Brazil (1) Indonesia (1) Poland (1) South Africa (1)	% Male: mean 55.6% Mean age onset (weighted): 28.2 yrs % schizophrenic: 88% Low Income Country: 40.7% Low /Middle Income: 25.3% Upper Middle Income: 34.0%	*Psychosis* Patients met criteria for diagnosis of psychotic disorder according to DSM or ICD classification systems. *DUP* Duration between first symptom treatment initiation; Duration of psychotic illness till 4 weeks of treatment; Onset of psychosis to contact with health authorities; Onset of delusions/ hallucinations to treatment (2); Duration between meeting criteria for schizophrenia and treatment; Duration between first psychotic symptom and entry into drug trial; Duration between onset of any psychotic symptom and presentation for treatment; Duration between definite psychosis measured by care givers and treatment; Period between first positive symptom estimated by senior psychiatrist and hospitalization. One study from China had no operational definition of DUP and included patients who had received traditional treatments.

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Lloyd-Evans et al. 2010 [9/11]*	11 studies evaluating 8 early detection initiatives.	Not reported.	Norway (3, all 3 evaluating same intervention); Australia (3, of which 2 evaluating same intervention); UK(2) Canada (1) Ireland (1) Singapore (1)	Health professionals (GPs), teachers, school children, general public The review included studies of interventions to promote identification and early access to treatment for people with first-episode psychosis (FEP). Studies concerning only populations with at-risk mental states but yet to develop psychosis, or people already being treated for psychosis, were excluded.	*Psychosis* Not defined. *DUP* Two studies did not report how DUP (period between onset of psychosis and start of treatment) was defined. Of the ten studies which measured DUP, six did not report using a published assessment tool to elicit information about DUP.

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Marshall et al. 2005 [9/11]*	26	4490	US (6) Germany (4) Canada (3) UK (2) Australia (1) Finland (1) France (1) India (1) Ireland (1) Mexico (1) Netherlands (1) Norway (1) Scandinavia (1) Spain (1) Turkey (1)	First-episode cohorts only. Studies excluded if were restricted to patients < 16 yrs or > 60 yrs. Mean age at presentation 27.8 yrs. % Male: 61% 20 studies restricted to participants with schizophrenia or schizophrenia-like disorders.	*Psychosis* Direct measures of psychopathologic characteristics were selected as the primary outcome variables because of their presumed proximity to the core disease process in schizophrenia. Measures included positive symptoms, negative symptoms, symptoms of depression/anxiety, all symptoms (defined as the combined score for negative, positive, and neurotic symptoms), overall functioning (as defined by the composite level of functioning scores on the Global Assessment of Functioning scale, the Global Assessment Scale, or similar scales). *DUP* Time from manifestation of first psychotic symptom to initiation of adequate antipsychotic drug treatment. Distinguished from duration of untreated illness, which has the same end point but begins with the emergence of the first symptom. 12 studies reported the use of a systematic method to assess DUP.

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Marshall and Rathbone 2011 [11/11]*	92 studies reporting on 18 randomized controlled trials	1808	Australia (6) UK (3) US (2) Germany (2) Austria (1) China (1) Netherlands (1) Scandinavia (1) Spain (1)	For trials to prevent the development of psychosis, we included people judged by trialists to be in prodromal phase of psychosis. For trials to improve outcome in FEP, we included people who were in their first episode of psychosis, or were in the process of recovering from their first episode. Trials excluded when the majority of participants suffering from learning disability/ organic psychosis. Trials excluded where >10% of participants had experienced a second episode.	*Psychosis* People with psychosis were defined as those presenting with any combination of delusions, hallucinations or thought disorder, or those who had been given a diagnosis of schizophrenia or schizophrenia-like disorder, bipolar disorder (manic episode i.e. with psychotic symptoms), or depression with psychotic features.

Systematic review (AMSTAR score)	No. included studies	Pooled no. of subjects	Countries	Participants	Disease State
Perkins et al. 2005 [6/11]	44	DUP and outcome in FEP: 5501 DUP and treatment response: 1915	US (9) Canada (7) UK (6) Norway (4) Australia (3) Germany (3) France (2) International (2) Europe: Spain and Finland (1) China (1) Denmark (1) Ireland (1) Netherlands (1) Singapore (1) Turkey (1)	Not reported.	*Psychosis* Studies were included where psychopathology was assessed by using clinician-rated instruments and the study reported subjects' diagnoses with most of the subjects meeting the standard diagnostic system criteria for a non-affective psychotic disorder.
This review satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool (see Appendix 2).					

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12.3 Prevalence

Estimates for DUP will vary widely across studies due in part to differences in definition and measurement (see Table 12.1 above). Nevertheless, Anderson et al. (2010) provided a summary measure of DUP i.e. the time interval between symptom initiation and diagnosis and/or treatment: they found a median of 21.6 weeks, with a range of four to 68 weeks.

12.4 Determinants

One review contributed to our understanding of the determinants of delayed diagnosis of psychosis (Anderson et al. 2010). Anderson and colleagues found that of the 30 studies included within their review, only nine examined the sex, socio-economic, and/or ethnic determinants of pathways to care of patients with FEP. None of the 30 primary studies included within the review by Anderson et al. (2010) were common to any of the other reviews included within our rapid review.

The determinants of pathways to care of patients with first-episode psychosis are presented in table 12.2 below

Table 12.2: Determinants of the pathway to care for patients with first episode psychosis (FEP).

Determinants	Anderson et al. (2010) No. of primary studies (n); Association: □ (Not predictive of care pathway)
Demographic	**Gender:** Male (3 □); Males less likely to be admitted by GP in UK (1); Males more likely to be admitted involuntarily in South Africa (1) Males five times more likely to make first contact with the emergency department in Canada(1); **Ethnicity** (3 □); Afro-Caribbean patients less likely to be referred by a GP and more likely to have police involvement on their pathway to care in UK (2); Longer treatment delays for Afro-Caribbean patients (1); Asian patients (not including Afro-Canadian) three to four times more likely to make first contact with emergency services than white patients in Canada (1); Differences in compulsory admissions for minority patients (3) **Socio-economic status** (5 □); Semi-skilled or those with no vocational training more likely to make first contact with police in Germany(1)
System	**Referral source and DUP** (2□) Canadian patients referred from in-patient units to EIS had significantly shorter DUP than patients referred by community agencies, psychologists, or psychiatrists (1);

Determinants	Anderson et al. (2010) No. of primary studies (n); Association: □ (Not predictive of care pathway)
	Longer delays in time to referral in Switzerland when referred by psychiatrist, psychologist, or non-physician service compared with referral by GP or psychiatric services (1); UK patients referred via home treatment or the emergency department had lowest DUP (1) **First point of contact and DUP** (2□) Canadian patients with non-physician first contact had a significantly longer DUP (1); US patients with GP first contact have longer treatment delays (1); Patients in France with private psychiatrist first contact have longer delays as compared to patients with GP or public psychiatrist first contacts (1); Patients in Germany having first contact with non-physicians or at hospital for another complaint have longer DUP compared with those making first contact with emergency services (2); DUP is longest for patients in China when the first contact is a psychiatrist or psychologist (1); No difference between making first contact with a traditional/ religious healer compared with other care pathway contact in Singapore (1).

Determinants: Key Findings

Demographic

- Gender: Three studies found no association between gender and care pathway. Males were less likely to be admitted by a GP in the UK. Two UK studies found evidence that gender may act as an effect modifier in the relationship between ethnicity and compulsory admission; however, the results were conflicting, with one finding ethnic differences for males and the other finding ethnic differences for females.

- Ethnicity: Of seven studies three found no evidence of ethnic differences. Two UK studies found that Afro-Caribbean patients were less likely to be referred by a GP and more likely to have police involvement on their pathway to care. A Canadian study found that Asian patients were three to four times more likely to make first contact with emergency services than white patients. Three of four studies reporting ethnic differences in the pathway to care also found evidence of differences in compulsory admissions for minority patients.

- Socio-economic status: Five studies found no evidence that socio-economic factors are predictive of the care pathway. Findings from a German study suggested that patients with semi-skilled or no vocational training were more likely to make first contact with police.

System

- Referral Source and DUP: Two of five studies found no significant association between referral source and DUP. A Canadian study found that patients referred from in-patient units to early intervention services had significantly shorter DUP, whereas patients referred by community agencies, psychologists, or psychiatrists had a significantly longer DUP. A Swiss study found delays to referral with psychiatrists, psychologists, or non-physician services as compared with GP or psychiatric services referral. Individuals referred via home treatment or the emergency department had the lowest DUP in a UK study.

- First point of contact and DUP: The overall picture with regard to first point of contact on the care pathway and DUP was mixed. Of ten studies, two found no significant association and a third had an insufficient sample for conclusions to be drawn. A Canadian study found that patients with non-physician first contact had significantly longer DUP. A US study demonstrated longer treatment delays when first contact was with a GP. A French study indicated longer delays when first contact was a private psychiatrist, as compared with a GP or public psychiatrist. A Chinese study also suggested that DUP is longest when the first care pathway contact is a psychiatrist or psychologist. One German study reported longer DUP where first contact was with non-physicians or at hospital for another complaint, and another German study reported shorter DUP for patients who made first contact with emergency services. A study from Singapore found no difference between making first contact with a traditional or religious healer as compared with those who sought help from another care provider.

12.5 Outcomes

Three of the included systematic reviews investigated the association of DUP with numerous outcomes including mortality, symptom severity, depression and anxiety, cognitive function, quality of life, social functioning and disability, and relapse risk and remission (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005). The primary studies common to more than one systematic review are highlighted in table 12.3 below.

As shown in table 12.3, there is substantial overlap of primary studies between Marshall et al. (2005) and Perkins et al. (2005), with 17 studies common to both. Marshall et al. (2005) did not always provide full details of the primary studies incorporated into separate meta-analyses and therefore it was not always possible to determine which primary studies were contributing to summary measures. The review by Farooq and colleagues shared only two studies in kind with the other reviews: one study (Tirupati et al. 2005) also appeared in Marshall et al. (2005), and one study (Lieberman et al. 2003) also appeared in Perkins et al. (2005).

Table 12.3: Primary studies common to more than one systematic review investigating the association of outcomes with DUP.

	Farooq et al. 2009 n=11	Marshall et al. 2005 n=26	Perkins et al. 2005 n=44
Primary studies			
Addington et al. 2004		x	x
Alpteckin et al. 2005	x		
Amminger et al. 2002			x
Apiquian et al. 2002,2006	x		
Archie et al. 2006			
Ayres et al. 2007	x		
Barnes et al. 2000		x	x
Black et al. 2001		x	x
Bottlender et al. 2000		x	x
Bottlender et al. 2002		x	
Bottlender et al. 2003			x
Browne et al. 2000		x	x
Carbone et al. 1999		x	
Craig et al. 2000		x	x
Crow et al. 1986			x
De Haan et al. 2003			x
Drake et al. 2000		x	x
Edwards et al. 2006			
Fannon et al. 2000			x
Fuchs and Steinert 2004		x	
Fresen et al. 2003		x	
Galinska et al. 2005	x		
Haas and Sweeney 1992		x	x
Harrigan et al. 2003			x
Ho et al. 2000a		x	x
Hoff et al. 2000b			x
Huber et al. 1975		x	
Huber et al. 1997			x
Joyce et al. 2002			x
Kalla et al. 2002		x	x
Keshavan et al. 2003		x	
Kua et al. 2003			x
Kurihara et al. 2006	x		
Larsen et al. 1996			x
Larsen et al. 2000		x	x
Lieberman et al. 2003	x		x
Loebel e al. 1992		x	
Madsen et al. 1999			x
Malla et al. 2002a		x	x
Malla et al. 2002b			x
Malla et al. 2002c			x
McGorry et al. 1996			x
Melle et al. 2004		x	x
Norman et al. 2004			x

	Farooq et al. 2009 n=11	Marshall et al. 2005 n=26	Perkins et al. 2005 n=44
Oosthuizen et al. 2005	x		
Perkins et al. 2004			x
Rabiner et al. 1986			x
Ran et al. 2001, 2003, 2007	x		
Ring et al. 1991			x
Robinson et al. 1999a			x
Robinson et al. 1999b			x
Rund et al. 2004			x
Szymanski et al. 1996		x	x
Thirthalli et al. 2005	x		
Tirupati et al. 2004	x	x	
Townsend et al. 2002			x
Ucok et al. 2004		x	x
Ucok et al. 2006	x		
Verdoux et al. 1998			x
Verdoux et al. 1999		x	
Verdoux et al. 2001			x
Wiersma et al. 1998		x	x
Wiersma et al. 2000			x

12.5.1 Mortality

Two primary studies within one review (Farooq et al. 2008) examined the relationship between DUP and mortality: Kurihara et al. (2006) and Ran et al. (2007). Kurihari et al. (2006) reported on the mortality of 59 consecutive Balinese FEP patients, with a follow-up period of 11 years. Patients with a DUP of >1 year had 6.7 times the mortality of those with DUP of < 1 year. Ran et al. (2007) also found that the mortality of Chinese patients with a long DUP was significantly higher than those who received treatment earlier. However, long DUP was also associated with inadequate treatment and since a minority of patients received ongoing treatment, an association between DUP and mortality could not be inferred.

12.5.2 Symptom Severity

Positive symptoms

Positive symptoms of schizophrenia are those characterised by a distortion of normal functioning, including disorganized thought processes and disorganized behaviour such as difficulty with personal care. Three reviews examined the association between DUP and the severity of positive symptoms (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005).

Farooq et al. (2008) conducted a meta-analysis of four studies (Apiquian et al. 2006, Galinska et al. 2005, Oosthuizen et al. 2005, Ucok et al 2006) which showed a negative association between DUP and positive symptoms at baseline [$r = -0.152$, 95% CI -0.280 to -0.02, $z = -2.248$, $p < 0.025$, heterogeneity Q-value 1.25, p = NS, I^2 = 0.00].

As shown in Table 12.4 below, Marshall et al. (2005) observed statistically significant correlations between duration of DUP and severity of positive symptoms at six, 12 and 24 months.

Table 12.4: Summary correlations between DUP and severity of positive symptoms at baseline, six, 12 and 24 months (Marshall et al. 2005).

	Baseline n=1135 subjects	6 months n=933 subjects	12 months n=777 subjects	24 months n=164 subjects
Correlation Coefficient (95% CI)	0.089 (-0.041 to 0.217)	0.295 (0.234 to 0.352)	0.283 (0.216 to 0.347)	0.170 (0.017 to 0.315)

Marshall et al. (2005) found that where data were available based on comparisons between groups categorised as having either long or short DUP, at first presentation there were no statistically significant differences between groups in terms of positive symptoms. The severity of positive symptoms was found to be worse in long DUP groups at six months. One study showed that there were no statistically significant differences between the long and short DUP groups for positive symptoms at 24 months. However another study with a follow-up of 15 years demonstrated that the long DUP group was significantly worse with regard to positive symptoms.

Perkins et al. (2005) presented combined summary statistics indicating that shorter DUP was associated with greater response to antipsychotic treatment as measured by positive symptom severity [Hedge's g = 0.51, 95% CI, 0.22 to 0.59, n=6; combined r = 0.27, 95% CI, 0.21 to 0.31, n=9]. Neither meta-analysis employed studies appearing in meta-analyses in the review by Farooq et al. (2008). Perkins et al. (2005) did not find DUP was related to the severity of positive symptoms at first treatment contact.

Taken together the results of the three reviews suggest that there is either no association or a weak negative association between DUP and severity of positive symptoms at presentation, but that longer DUP is associated with greater severity of positive symptoms after treatment.

Negative symptoms
Negative symptoms of schizophrenia include a lack of emotional response, poverty of speech and absence of will. Negative symptoms may be more difficult for doctors to evaluate than positive symptoms. Three reviews examined the association between DUP and the severity of negative symptoms (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005).

Farooq et al. (2008) conducted a meta-analysis of three studies (Galinska et al. 2005, Oosthuizen et al. 2005, Ucok et al. 2006) which showed that longer DUP was not associated with the extent of negative symptoms at baseline. [r = -0.057, 95% CI -0.0101 to 0.211, z = 0.705, p< 0.048, heterogeneity Q-value 1.01, p = NS, I^2 = 0.00].

As shown in table 12.5 below, Marshall et al. (2005) observed statistically significant correlations between duration of DUP and severity of negative symptoms at six and 12 months only.

Table 12.5: Summary correlations between DUP and severity of negative symptoms at baseline, six, 12 and 24 months (Marshall et al. 2005)

	Baseline n=1401 subjects	6 months n=933 subjects	12 months n=779 subjects	24 months n=164 subjects
Correlation Coefficient (95% CI)	0.082 (-0.016 to 0.179)	0.242 (0.180 to 0.302)	0.176 (0.106 to 0.244)	-0.110 (-0.259 to 0.044)

Marshall et al. (2005) found that where data were available based on comparisons between groups categorised as having either long or short DUP, there were statistically significant differences between groups in terms of negative symptoms only at first presentation (longer DUP group with more severe negative symptoms).

Perkins et al. (2005) presented combined summary statistics indicating that shorter DUP was associated with greater response to antipsychotic treatment as measured by negative symptom severity by collating data from fourteen studies (Addington et al. 2004, Black et al. Bottlender et al. 2000, Bottlender et al. 2003, Craig et al. 2000, 2001, Harrigan et al. Ho et al. 2001, 2003, Larsen et al. 2000, Malla et al. 2002a, Malla et al. 2002b, Melle et al. 2004, Perkins et al. 2004, Ring et al. 1991, Ucok et al. 2004) [Hedge's g = 0.3, 95% CI 0.14 to 0.46, n=8; r = 0.23, 95% CI 0.17 to 0.27, n=8]. However, Perkins et al. (2005) also found that longer DUP was significantly associated with greater severity of negative symptoms at first treatment contact [Hedge's g = 0.28, 95% CI 0.1 to 0.45; r = 0.15, 95% CI 0.09 to 0.21].

The results of the three reviews are mixed and conflicting with regard to the association between DUP and the severity of negative symptoms.

Combined Symptom Scores

Three reviews examined the association between DUP and combined symptom scores (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005).

Farooq et al. (2008) presented results from a meta-analysis of five studies (Apiquain et al. 2006, Lieberman et al. 2003, Oosthuizen et al. 2005, Thirthali et al. 2005, Ucok et al. 2006) which indicated that longer DUP was negatively associated with the degree of reduction in symptom scores [random effects model, r = -0.290, 95% CI, -0.483 to -0.069, z = -2.559, p<0.011].

Perkins et al. (2005) presented combined summary statistics indicating that shorter DUP was associated with greater response to antipsychotic treatment as measured by improvement or endpoint severity of global psychopathology by aggregating data from five studies (Black et al. 2001, Drake et al. 2000, McGorry et al. 1996, Perkins et al. 2004, Ucok et al. 2004) [Hedge's g = 0.51, 95% CI 0.33 to 0.69, n=4; r = 0.29,

95% CI 0.2 to 0.36, n=3]. One study within Perkins et al. (2005), using a modified Global Assessment of Functioning tool in which symptoms and function were rated separately, found duration of untreated psychosis to be significantly associated with 3-month global symptom severity [r = –0.41, p<0.01].

Marshall et al. (2005) presented a summary correlation between DUP and "all symptoms" (defined as the combined score for negative, positive and neurotic symptoms) which was non-significant at first presentation [r = -0.02, 95% CI, -0.100 to 0.060]. However, by six and 12 months there were statistically significant correlations between DUP and "all symptoms" where longer DUP was associated with a worse outcome. Results from data based on comparisons between groups categorised as having either long or short DUP were consistent with those from correlational data. At first presentation the differences between the long and short DUP groups were not statistically significant [standardised mean difference = -0.59, 95% CI, -0.545 to 1.417]. However, by 6 months there was a statistically significant difference between the long and short DUP groups for "all symptoms" [standardised mean difference = 0.322, 95% CI, 0.56 to 0.589].

Taken together the results of the three reviews suggest that longer DUP is associated with greater severity of global symptoms after treatment.

12.5.3 Depression/Anxiety

One review presented results regarding the association between DUP and depression/anxiety (Marshall et al. 2005).

As shown in table 12.6 below, Marshall et al. (2005) observed statistically significant correlations between duration of DUP and depression/anxiety at six and 12 months (longer DUP group with greater severity of depression/anxiety). Results from data based on comparisons between groups categorised as having either long or short DUP showed that, as with most other outcomes in the study, there was no statistically significant difference at baseline between long and short DUP groups. The authors also failed to find a statistically significant difference in depression/anxiety between long and short DUP groups at six months, although data were limited to only 19 patients for this outcome.

Table 12.6: Summary correlations and standardised mean difference between DUP and depression/anxiety at baseline, six and 12 months (Marshall et al. 2005)

	Baseline	6 months	12 months
n=participants Correlation Coefficient (95% CI)	n=571 0.107 (0.025 to 0.188)	n=530 0.220 (0.137 to 0.300)	n=376 0.194 (0.094 to 0.291)
n=participants Standardised Mean Difference (95% CI)	n=72 -1.05 (-0.578 to 0.368)	n=19 0.272 (-0.698 to 1.241)	-

12.5.4 Cognitive function

Two reviews presented results regarding the association between DUP and cognitive function (Farooq et al 2008, Perkins et al. 2005).

Farooq et al. (2008) included two studies which examined the effects of DUP on cognitive function at baseline. There was insufficient data for meta-analysis, but neither study (Ayres et al. 2007, Galinska et al. 2005) found an association between DUP and cognitive function.

Perkins et al. (2005) reported upon nine studies examining the relationship between DUP and neuro-cognitive function. Of nine studies, only two found that longer DUP was associated with worse cognitive performance: Amminger et al. (2002) demonstrated that longer DUP was associated with estimated cognitive decline before treatment as measured by the Wechsler Adult Intelligence Scale (WAIS) , whereas Joyce et al. (2002) found that there was a significant relationship between DUP and neuro-cognitive function when measuring aspects of executive function as assessed by the Cambridge Neuropsychological Test Automated Battery. However, the authors note that in an earlier analysis (Barnes et al. 2000) of a subsample from this same study (the West London First Episode Study) no associations were found between DUP and IQ or intellectual decline from the premorbid level, oculomotor functioning, memory, attention, or executive function.

Taken together, the results of these two reviews provide weak evidence to suggest that there is no relationship between DUP and cognitive function.

12.5.5 Quality of Life

Two reviews presented results regarding the association between DUP and quality of life (QOL) (Marshall et al. 2005, Perkins et al. 2005).

As shown in table 12.7 below, Marshall et al. (2005) observed statistically significant correlations between DUP and QOL at baseline, 12 and 24 months. Results from data based on comparisons between groups categorised as having either long or short DUP showed a significant difference between long and short DUP groups (longer DUP associated with lower QOL) at both baseline and six months.

Table 12.7: Summary correlations and standardised mean difference between DUP and quality of life (QOL) at baseline, six, 12 and 24 months (Marshall et al. 2005)

	Baseline	6 months	12 months	24 months
n=participants Correlation Coefficient (95% CI)	n=330 0.188 (0.081 to 0.290)	n=74 -0.100 (-0.321 to 0.132)	n=403 0.251 (0.157 to 0.340)	N=164 0.200 (0.048 to 0.343)
n=participants Standardised Mean Difference (95% CI)	n=53 0.804 (0.247 to 1.360)	n=200 0.337 (0.210 to 0.465)	-	-

Perkins et al. (2005) reported individual results from four studies examining the association between DUP and quality of life. Two studies found that DUP was associated with Heinrich-Carpenter QOL at 1-year follow-up [r = -0.29, p = 0.001] (Harrigan et al. 2003) and 2-year follow-up [r = -0.20, p < 0.05] (Addington et al. 2004). However, Perkins et al. (2004) failed to establish a relationship between DUP and Heinrich-Carpenter QOL at 2-year follow-up. Malla et al. (2002) reported a significant relationship between DUP and Wisconsin QOL Index scores at 1-year follow-up, but this relationship did not remain significant in a regression model that included the variables of pre-morbid adjustment, residual symptom severity, and adherence to medication.

The results of the two reviews are mixed and conflicting with regard to the association between DUP and quality of life.

12.5.6 Social functioning and disability
Three reviews presented results regarding the association between DUP and social functioning/ disability (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005).

Farooq et al. (2008) presented a pooled estimate from four studies from Turkey, Mexico, China and India respectively (Alptekin et al. 2005, Apiquian et al. 2006, Ran et al. 2007, Tirupati et al. 2004) suggesting that there was a significant association between longer DUP and a greater level of disability [r = 0.195, 95% CI, 0.126 to 0.262, z = 5.498, p < 0.0001, Q-value 1.245, p = NS, I^2 = 0.00].

As shown in table 12.8 below, Marshall et al. (2005) observed statistically significant correlations between DUP and social functioning at six and 12 months only.

Table 12.8: Summary correlations between DUP and social functioning at baseline, six, 12 and 24 months (Marshall et al. 2005)

	Baseline n=248 subjects	6 months n=108 subjects	12 months n=191 subjects	24 months n=55 subjects
Correlation Coefficient (95% CI)	0.040 (-0.085 to 0.164)	0.199 (0.008 to 0.377)	0.234 (0.093 to 0.366)	0.190 (-0.079 to 0.433)

Marshall et al. (2005) also presented pooled estimates for "overall functioning" (defined by composite level of functioning scores on the Global Assessment of Functioning scale, the Global Assessment Scale or similar scales). The authors presented a summary correlation between DUP and overall functioning which was non-significant at first presentation [r = -0.014, 95% CI, -0.117 to 0.090, n=367]. However, by six, 12 and 24 months there were statistically significant correlations between DUP and overall functioning where longer DUP was associated with a worse outcome [6 months: r = 0.200, 95% CI, 0.127 to 0.271, n=684; 12 months: r = 0.277, 95% CI, 0.165 to 0.382, n=287; 24 months: r = 0.280, 95% CI, 0.045 to 0.486,

n=68]. Results from data based on comparisons between groups categorised as having either long or short DUP were consistent with those from correlational data. At first presentation the differences between the long and short DUP groups were not statistically significant [standardised mean difference = -0.112, 95% CI, -0.344 to 0.120, n=290]. However, by 6 months there was a statistically significant difference between the long and short DUP groups for overall functioning [standardised mean difference = 0.374, 95% CI, 0.135 to 0.613, n=272].

Perkins et al. (2005) reported the individual results of four studies evaluating the association between DUP and functional outcomes (Melle et al. 2004, Kua et al. 2003, Wiersma et al. 2000, Ho et al. 2000). Melle et al. (2004) found DUP was significantly associated with global functional outcomes [r =–0.30, p<0.01] using a modification of the Global Assessment of Functioning (GAF) scale. Kua et al. (2003), demonstrated with logistic regression modelling that DUP was significantly related to function as measured by the Global Assessment Scale (GAS) at five, ten, 15 and 20-year follow-up [OR = 1.84–4.91, p<0.05]. Wiersma et al. (2000) found that DUP was related to overall function as measured by the WHO Disability Assessment Schedule at two and 15-year follow-up. However, in a study that included the "Psychiatric Status You Currently Have" interview, Ho et al. (2000) found no relationship between DUP and six month social and vocational outcomes. Perkins et al. (2005) also found that DUP was not significantly associated with global assessments of function (assessed with GAF or GAS) at first treatment contact.

The results of the three reviews are inconsistent, but provide some evidence for an association between DUP and reduced social functioning.

12.5.7 Relapse risk and remission
Three reviews examined the association between DUP and relapse risk or remission (Farooq et al. 2008, Marshall et al. 2005, Perkins et al. 2005).

One primary study within the review by Farooq and colleagues found that in rural China, 35% of patients with a DUP of less than a year had complete remission compared with only 7% of patients with a DUP of more than a year (Ran et al. 2003).

Marshall et al. (2005) included seven studies (Black et al. 1998, Bottlender et al. 2002, Verdoux et al. 1999, Tirupati et al. 2004, Malla et al. 2002, Craig et al. 2000, Huber et al. 1975) which provided data on the number of patients in remission in long and short DUP groups. Participants with long DUP were significantly less likely to achieve remission at all follow-up [6 months combined OR = 3.55, 95% CI, 2.03 to 6.18, n=266; 12 months combined OR = 2.75, 95% CI, 1.14 to 6.64, n=133; 24 month combined OR = 2.72, 95% CI, 1.20 to 6.17, n=206]. Huber et al. (1975) found that patients were almost 2 and a half time less likely to report no symptoms at interview after 269 months if they were in a long DUP group rather than a short DUP group.

Two studies (Larsen et al. 2000, Carbone et al. 1999) provided data on length of DUP among participants in remission vs participants not in remission. These data

showed that DUP was significantly longer in patients not in remission (standardized mean difference = 0.517, 95% CI, 0.121 to 0.915, p =0.01, heterogeneity NS, n=270]. Two studies (Wiersma et al. 1998, Loebel et al. 1992) provided data on time to remission, and both showed that it was longer among participants with long DUP. Loebel et al. (1992) also showed that the likelihood of remission is reduced in patients with a DUP greater than 1 year, although risk of relapse is not increased.

Perkins et al. (2005) found that five studies examining the association between DUP and relapse risk showed mixed results. In a study using parent and self-report ratings to evaluate psychopathology and DUP, a significant relationship was found between longer DUP and relapse risk (assessed by chart review) at six year follow-up (de Haan et al. 2003). Verdoux et al. (2001) found that this relationship approached significance (p = 0.08) at two year follow-up. In a prospective two-year study comparing maintenance antipsychotic medication to placebo, Crow et al. (1986) found a high relapse rate in both antipsychotic-treated (45%) and placebo (62%) groups: DUP before initiation of antipsychotic treatment predicted relapse in both groups. However, two further studies found no relationship between DUP and risk of relapse after recovery from first episode psychosis (Robinson et al. 1999, Wiersma et al. 1998).

Taken together the results of the three reviews suggest that longer DUP is associated with a greater likelihood of relapse and lower rates of remission.

12.6 Costs Implications

None of the included reviews presented data regarding the cost implications of prolonged DUP. A UK economic evaluation suggests that early intervention results in cost savings – see section 12.8.

12.7 Interventions

Three reviews examined interventions to reduce DUP or delayed diagnosis of psychosis (Bird et al. 2010, Lloyd-Evans et al. 2011, Marshall and Rathbone 2011).

Lloyd-Evans et al. (2011) concentrated on programmes that aimed to improve the early identification of symptoms by GPs, teachers, students, youth workers, parents and the general public, and typically included reports of training, information and public awareness campaigns. The other two reviews investigated the effectiveness of early intervention programmes, for people who have experienced a first episode of psychosis. Additionally Marshall and Rathbone (2011) reported on studies aiming to prevent transition to psychosis for people with prodomal symptoms. These initiatives, often using a case management paradigm, include medication, family and personal counselling and psychotherapy (usually cognitive behavioural therapy (CBT)), and psycho-social interventions, such as education or employment support.

As shown in table 12.9 below, only four primary studies were common to more than one of the included systematic reviews evaluating the effect of interventions to reduce delayed diagnosis of psychosis (Leavey et al. 2004, Petersen et al. 2005a, Power et al. 2007, Zhang et al. 1994). Bird et al. (2010) and Marshall and Rathbone

(2011) had three primary studies in common: (Leavey et al. 2004, Petersen et al. 2005a, Zhang et al. 1994). Power et al. (2007) was found in two reviews (Marshall and Rathbone 2011, Lloyd-Evans et al. 2010).

Table 12.9: Primary studies common to more than one systematic review investigating interventions to address DUP or delayed diagnosis of psychosis.

	Bird et al. 2010 n=11	Lloyd-Evans et al. 2011 n=11	Marshall and Rathbone 2011 n=92
Primary studies			
Leavey et al. 2004	x		x
Petersen et al. 2005a	x		x
Power et al. 2007		x	x
Zhang et al. 1994	x		x

12.7.1 Experimental Reduction of DUP

Lloyd-Evans and colleagues reported on eight initiatives (one project, TIPS, was evaluated three times) to improve the prompt identification of psychotic symptoms. Three of these were GP education campaigns, one was a service reconfiguration, and four were multi-focus awareness campaigns targeting doctors and health professionals as well as teachers, students and the broader public. The campaigns utilised a variety of media, such as creating a TV docu-drama, distributing leaflets, advertising in newspapers and on the radio, to inform their audiences about symptoms and the importance of early treatment, as well as presenting a non-stigmatizing image of psychosis and mental health services. Workshops were run for GPs at their practices, and two of the programmes provided follow-up contact. The service configuration involved the set up of a dedicated service for people with first episode psychosis to provide a clear point of referral and swift service response.

The outcomes measured by the evaluations were: reductions to DUP; referral or treatment rate; pathways to care; health status at admission; and the behaviour of referrers. The results of these evaluations are presented in table 12.10.

Of the 11 included studies, two were cluster randomised trials, two were prospective two-group natural experiments, and seven retrospectively compared two groups or one group with a historical comparison. Lloyd-Evans et al. (2010) noted several problems with the quality of the studies, including: no measurement of differences between groups in the non-randomised trials; the retrospective nature of the studies; attrition rate, only six of ten studies that measured DUP obtained data from over 60% of eligible patients; lack of definition of DUP; and use of unpublished assessment tools for information about DUP. Three studies were of good quality, REDIRECT (Lester et al. 2009), TIPS (Melle et al. 2004), EPPIC 2 (Krstev et al. 2004), as they were of prospective design, had data from adequate numbers of participants and defined how DUP was measured.

Results from the four studies investigating multi-focus public awareness campaigns to reduce DUP are equivocal. Two studies (TIPS and EPIP) show a reduction in DUP, while two (EPPIC2 and PEPP) do not. The authors point to the difference in intensity, the targeting of the general public as well as doctors, greater use of mainstream media and more emphasis on help seeking behaviour and changing attitudes to psychosis, as reasons for the success of the two campaigns in comparison to the other two which aimed to increase knowledge of symptoms and services. However, patients have less severe symptoms at hospital admission in the intervention areas where this was measured (TIPS, EPPIC2). Workshops for doctors may improve the pathway into care, with more patients being referred to mental health services, more quickly.

Table 12.10: Outcomes of Training and Public Awareness Campaigns

Name of initiative (country)	Description	No. of referred patients in treatment/control group	Reductions in DUP	Referral / treatment rate	Pathways to care	Health status at admission	Referrers behaviour
TIPS (Norway)	Multifocus awareness campaign	First evaluation: 60/43 Third evaluation: 108/75	Significant reductions in mean and median DUP from all evaluations (p=0.005, P=0.003, p<0.005)	Similar incidence rates of treated cases in intervention and comparison regions (intervention – 50:100,000 v. control – 66:100,000)		Significantly less severe symptoms for those in intervention group	
EPIP (Singapore)	Multifocus awareness campaign	287/107	Significant reductions in mean and median DUP (p=0.002)		Patients significantly more likely to self refer and less likely to be referred by police		
EPPIC1 (Australia)	Service reconfiguration	51/51	No significant difference				
EPPIC2 (Australia)	Multifocus awareness campaign,	40/58	No significant difference in proportion of patients with DUP<1 year, but significantly			Significantly less severe symptoms for those in intervention group	

Name of initiative (country)	Description	No. of referred patients in treatment/control group	Reductions in DUP	Referral / treatment rate	Pathways to care	Health status at admission	Referrers behaviour
			more patients in intervention group with DUP >3years				
PEPP (Canada)	Multifocus awareness campaign	-	No significant difference	Similar incidence rates of treated cases in intervention and comparison regions (intervention – 27.5:100,000 v. control – 26:100,000)	No significant difference with comparison groups in referral source	No significant difference in patients' symptom severity between intervention and comparison areas	
LEOCAT (UK)	Doctor education	36/35	No significant difference Significantly fewer patients in intervention group (6% v. 27%) experienced delays of longer than 6 weeks		Patients from practices in intervention group less likely to have contact with Accident and Emergency departments on their pathway to mental health services		GPs more likely to refer people with first episode psychosis to mental health services

Name of initiative (country)	Description	No. of referred patients in treatment/control group	Reductions in DUP	Referral / treatment rate	Pathways to care	Health status at admission	Referrers behaviour
REDIRECT (UK)	Doctor education	47/36	No significant difference	No significant difference in no. of referrals from GP practices in intervention and control groups	No significant difference with comparison groups in referral source	No significant difference in symptom severity or pre-morbid adjustment between patients from GP practices in the intervention area and the comparison	Time from patients' first contact with GPs to referral to early intervention services significantly shorter for patients from surgeries in intervention arm of the study (P=0.002)
DETECT (Ireland)	Doctor education	-	No significant difference				GPs more likely to refer people with first episode psychosis to mental health services

12.7.2 Specialised Early Intervention Services (EIS) and Interventions in First Episode Psychosis (FEP)

Bird et al. (2010) and Marshall and Rathbone (2011) reviewed the evidence for early intervention on outcomes of psychosis. Bird and colleagues reported the results of four randomised controlled trials (RCTs) which examined the effectiveness of early intervention services, described as a package of case management, medication management, a range of psychosocial interventions including CBT, social skills training, family interventions (counselling), and vocational strategies such as supported employment. Additionally, they looked in more detail at CBT (four studies) and family interventions (three studies).

Marshall and Rathbone (2011) reported on 12 RCTs which were carried out to improve outcomes for people with first episode psychosis. Their review examined a wide range of interventions including CBT (two studies), family support (three studies), E-EPA oil (one study), psychotherapeutic and social support (four studies), specialised teams (one study) and crisis assessment (one study).

Bird et al. (2010) carried out a meta-analysis of the results from four early intervention services, and specifically reported on relapse rates, hospital admission, symptom severity, the rate of discontinuation of treatment, the likelihood of remaining in contact with services and the likelihood of receiving a psychosocial intervention. Generally, they found effects favouring the intervention for all these outcomes at the end of the treatment period. Findings are presented in table 12.11 below.

Table 12.11: Findings from trials investigating EIS for psychosis (Bird et al. 2010)

Outcome	No. of Trials	Participants, n: treatment/control	Summary of findings
Hospital admission	3	342/280	RR 0.67 (95% CI 0.54 to 0.83) 28.1% v. 42.1% NNT = 7, 95% CI 5 to 7
Relapse	2	91/81	RR 0.66 (95% CI 0.47 to 0.94) 35.2% v. 51.9% NNT = 6, 95% CI 3 to 25
Positive symptoms (PANSS or SAPS)	2	260/208	SMD -0.21 (95% CI -0.42 to -0.01)
Negative symptoms (PANSS or SANS	2	260/208	SMD -0.39 (95% CI -0.57 to -0.20)
Not receiving a psychological intervention	3	344/286	RR 0.67 (95% CI 0.46 to 0.97) 36.6% v. 14.0% NNT = 5, 95% CI 4 to 6
Not in contact with index team	2	314/266	RR 0.60 (95% CI 0.39 to 0.92) 91.4% v. 84.2% NNT = 13, 95% CI 4 to ∞
Leaving the study early for any reason	4	408/392	RR 0.71 (95% CI 0.53 to 0.94) 27.0% v. 40.5% NNT = 8, 95% CI 5 to 14

Marshall and Rathbone (2011) add some detail for the OPUS study (Petersen et al. 2005a) and the LEOCAT initiative (Craig et al. 2004), which are included in the results above. For OPUS, a study comparing specialised teams with standard care, they found that some outcomes were not maintained at significantly different levels at five years, i.e. leaving the study early [RR 1.01 95% CI 0.8 to 1.2], not hospitalised [RR 1.05 95% CI 0.90 to 1.2], Global Assessment of Functioning scores (equivocal) or at two years, i.e. compliance with treatment [RR 0.66 95% CI 0.3 to 1.5]. Social outcomes improved over time, with those in the intervention group more likely to live independently at five years [RR 0.42 95% CI 0.21 to 0.8, NNT 19 95% CI 14 to 62], and more likely to be working or in education at two years [RR 0.72 95% CI 0.5 to 1.0, NNT 11 95% CI 7 to 99], although this advantage had diminished by five years. Satisfaction with levels of care was greater for the intervention group and this was maintained into the second year [WMD -3.20 95% CI -4.1 to -2.3].

In the LEOCAT study, reported on by the two other reviews in this section, Marshall and Rathbone (2011) looked at crisis assessment specifically as compared with standard care. They found no significant difference in the number of people being admitted to hospital who had received a crisis assessment as compared with those who had not, (RR 0.85 95% CI 0.6 to 1.3), and the assessment did not result in significantly more people being referred to the mental health services by accident and emergency departments (RR 0.85 95% CI 0.6 to 1.3).

In conclusion, the meta-analysis of Bird and colleagues found that EIS impacted positively on a range of outcomes, such as hospital admission, relapse, positive and negative symptoms, the likelihood of receiving a psychological intervention and remaining in contact with mental health services, and study attrition. They only analysed these outcomes at the end of the treatment, while Marshall and Rathbone (2011), for one large study, the OPUS study (Petersen et al. 2005a) showed that some of these gains were not maintained at two or five years.

Cognitive Behavioural Therapy (CBT)

Bird and colleagues combined the results of four trials to assess the impact of CBT on symptom severity, relapse and hospital admission. They found no significant difference between the intervention and control groups for mean positive [pooled SMD -0.05, 95% CI -0.22 to 0.12] or negative symptoms [pooled SMD -0.03, 95% CI -0.17 to 0.23] at the end of the treatment, but at up to two years post treatment follow-up, CBT produced significantly reduced mean positive symptoms [pooled SMD -0.60, 95% CI -0.79 to -0.41] and negative symptoms [pooled SMD -0.45 95% CI -0.80 to -0.09].

CBT did not have an impact on relapse within the two year follow up period [RR 0.67 95% CI 0.24 to 1.85, 27.8% v. 32.2%, p=0.44] or on hospital admissions [RR 1.01 95% CI 0.76 to 1.35, 38.4% v. 38.5%, p=0.94].

Marshall and Rathbone (2011) reported on two trials that tested the effect of CBT on improving the outcomes at the first episode of psychosis. One of these (Jackson et al 2008) included the use of anti-psychotics as well as CBT. These results are presented in table 12.12.

Table 12.12: Outcomes for Cognitive Behavioural Therapy

Initiative (Country)	Sample Size	Leaving the Study Early	Hospital Admission	Suicide	Social Functioning
LifeSPAN (Australia)	56	No significant difference (RR 2.02 95% CI 0.7 to 5.7)		Two people died during the 6 month study – one from each group	
Jackson et al 2008 (Australia)	62	No significant difference between groups (RR 0.57 95% CI 0.2 to 1.8)	No significant differences in no. of participants being hospitalized over 12 months (RR 1.08 95% CI 0.59 to 1.99)	Two people died in the CBT group and none from the befriending group – not a significant difference.	No significant difference in mean total end-point scores from SOFAS social functioning scale (RR 1.30 95% CI -6.3 to 8.9) by 12 months. No significant differences in SOFAS positive and negative symptom scores.

To summarise, after meta-analysis, Bird et al. (2010) were able to conclude that CBT ameliorated positive and negative symptoms at the two year follow up, but not significantly at the end of the treatment. Marshall and Rathbone's analysis of two trials with small samples showed that there was no significant difference between the comparison groups for a range of outcomes, including hospital admission, suicide and social functioning.

Family Interventions

There were four trials testing interventions with families, with an overlap of two between the reviews. The interventions included elements of psycho-education, problem solving and crisis management. Families either had sessions separately or were in larger groups of families. Bird and colleagues' combined analysis from two trials showed that patients receiving a family intervention were less likely to relapse or be admitted to hospital compared to the control group (RR 0.50 95% CI 0.32 to 0.80, 14.5% v. 28.9% NNT = 7, 95% CI 4 to 20). One trial, Goldstein et al. (1978), just examined relapse at the end of treatment and at 6 months follow-up, and results from this are presented in table 12.13.

Marshall and Rathbone analysed the results from three trials and two of these, Leavey et al. (2004) and Zhang et al. (1994), were also included in Bird et al. (2010). All three of the interventions were designed to improve outcomes in first episode psychosis. The results of the trials are reported in table 12.13.

Both reviews considered family interventions promising for the avoidance of hospital admission and relapse and possibly the improvement of compliance with medication regimes.

Table 12.13: Outcomes for Family Interventions

Study (Country)	Sample size	Leaving the study early	Hospital admission	Compliance with medication	Relapse
Goldstein et al. 1978 (USA)	104				No significant differences but a suggested trend favouring intervention End of study: RR 0.58 CI 0.25 to 1.36) Up to 2 years follow up: RR 0.75 CI 0.39 to 1.43 (intervention group a numerically lower risk of relapse 23.1% v. 30.8%, p=0.38)
Leavey et al. 2004 (UK)	106	No significant differences in no. of people leaving the study early by nine months (RR 0.72 CI 0.3 to 1.5)	No significant differences: Before 4 months: RR 1.19 CI 0.9 to 1.6) Up to 4 months: RR 0.75 CI 0.4 to 1.4) Between 4 and 9 months: RR 0.86 CI 0.4 to 1.7)		
Zhang et al. 1994 (China)	83	No significant difference in the no. of people lost to follow up for 2 groups (RR 1.46 CI 0.3 to 8.3)	Participants receiving intervention significantly less likely to be admitted to hospital at 18 months than standard care control group (RR 0.28 CI 0.1 to 0.6. NNT 3 CI 2 to 6)	No significant difference in no. of people not compliant with medication at 18 months, although data suggested trend favouring intervention (p=0.06, RR 0.57 CI 0.3 to 1.0)	
Linszen et al. 1998	76				No significant difference between intervention and control groups at 12 months (RR 1.05 CI 0.4 to 3.0)

E-EPA Oil

There was one trial using E-EPA oil, otherwise known as Omega 3 fatty acids. In this study, participants in the intervention group and control were also given anti-psychotic drugs. Study attrition was equivocal, and those given E-EPA oils had similar rates of non-response to treatment (18/40) than the control (20/40) (RR 0.90 95% CI 0.6 to 1.4).

Psycho-social and Behavioural Interventions

There were four trials reported in Marshall and Rathbone (2011) that used behavioural therapies other than CBT.

Adherence Coping Education, reported on by Uzenoff et al. (2008), is an intervention designed to promote adherence to medication, to plan for maintenance treatment and to support rehabilitation. The comparison group in this study received emotional support. There were no significant differences between the two groups in relation to study attrition at six months [n=24, RR 1.27 95% CI 0.3 to 6.3], PANSS positive, negative, general or total scores [n=17, MD -1.57 95% CI -7.7 to 4.5], or depression rating [n=17, MD -1.46 95% CI -4.2 to 1.3]. Quality of life scores as measured by the Heinrichs-Carpenter scale were equivocal [n=16 MD -2.93 95% CI -25.6 to 19.7].

Cannabis and psychosis therapy was given with antipsychotics in an intervention reported on by Edwards et al. (2006), and the control group received psycho-education and antipsychotics. The therapy consisted of CBT as well as educational sessions, motivational interviewing, goal setting, and discussion about relapse prevention. The psycho-education sessions explained psychosis, medication and other treatments, and relapse. The sample was 47. There was no significant difference between the groups reported on any of the outcomes measured, which included cannabis use, knowledge of psychosis, mental state (positive and negative symptoms, and depression) and social functioning.

Killackey et al. (2008) described a trial of employment support, with a control group getting treatment as usual. From a sample of 41, participants with the vocational intervention were more likely to be employed [RR 0.39, 95% CI 0.21 to 0.7 NNT 2 95% CI 2 to 4], and there were no significant differences in study attrition by six months [RR 0.21 95% CI 0.03 to 1.6].

First episode participants were randomised to three different antipsychotics (risperidone, olanzapine, haloperidol) and then randomised to either Early Behavioural Intervention or routine care, in a trial described by Alvarez et al. (2005). The outcome measured was weight gain, and there was no appreciable difference between the two groups. The sample size was 61.

12.7.3 Summary of Interventions for Improving Outcomes of FEP

In their assessment of the 12 trails in their review, Marshall and Rathbone (2011) noted the small sample size of most of the trials, and so many of the outcomes may not be significant because the trials were underpowered. One large study of 547 participants, OPUS (Petersen et al. 2005a), which scored highly in their quality assessment process, was able to demonstrate the value of specialised teams.

The strategy of meta-analysis, adopted by Bird et al. (2010), yielded bigger amalgamated sample sizes and they were able to demonstrate positive results for early intervention services, CBT and family interventions.

The information presented in both reviews suggests that specialised teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, larger trials are needed to confirm this.

12.7.4 Preventing transition in high risk of psychosis groups
Identifying individuals with symptoms that then progress to a psychotic illness is complex and still the subject of research (Yung and McGorry 2007). The advantages of doing so consistently would mean that sufferers can be treated earlier and this may prevent progression to subsequent stages of the illness. However, many of the signs of the prodomal stages of psychosis are non-specific and could relate to a number of conditions, including depression, substance misuse and physical illness. Yung and McGorry (2007) have called for more research to identify those symptoms that are most predictive of future psychosis. The results from the six trials, reported on below by Marshall and Rathbone (2011), should be read with this in mind.

CBT
There were two trials that investigated the impact of CBT on people with prodomal symptoms. EDIE UK found that the people remained in the study but that there was no difference between the control and the intervention groups in terms of transition to psychosis during the 12 months of the study (EDIE-UK, n=60, RR 0.50 CI 0.2 to 1.7).

EIPS-Germany found no differences between the comparison groups in the outcomes of social activities, well being or employment. There was no significant difference in Global Social Adjustment scores either (EIPS-Germany, n= 69, WMD -0.10 CI -0.4 to 0.2).

Anti-Psychotic Medication
Marshall and Rathbone (2011) included 2 trials of anti-psychotic medication, namely olanzapine and amisulpride, conducted in the USA and Germany respectively.

The amisulpride study included a needs focus intervention which was used with the control group. This trial, sample size 102, was broadly favourable, showing reduced positive symptoms for the intervention group [PANSS-G, WMD -3.40 95% CI -6.9 to 0.1; PANSS +ve, WMD -2.10 95% CI -3.7 to -0.5] but no significant difference for negative symptoms and depression scores between the two comparison groups. Global Assessment of Functioning also favoured the amisulpride plus the needs focused intervention group [WMD -6.10 95% CI -11.8 to 0.5], and fewer participants dropped out of this group [RR 0.59 95% CI 0.4 to 0.9, NNT 5 95% CI 4 to 34].

In the olanzapine study (sample size 59-60), both groups had non-specific supportive therapy, and the control had a placebo instead of olanzapine. Participants were measured on a variety of outcomes, including leaving the study early, conversion to psychosis, global state, mental state and adverse effects. Slightly fewer people converted to psychosis in the olanzapine group [8/31 v. 13/29] but this was not statistically significant [RR 0.58 95% CI 0.3 to 1.2]. The tests of global state and mental state did not show a clear advantage to the intervention group, and there was no significant difference between the two groups in the number of people who remained in the study. The olanzapine group did experience adverse effects, with a significant weight gain by 12 months [WMD 7.63 95% CI 4.0 to 11.2], and the number of participants suffering from fatigue higher in the olanzapine group compared to the placebo [RR 8.42 95% CI 1.1 to 62.4, NNH 4 95% CI 2 to 211].

E-EPA Oil
This trial, conducted in Austria with a sample size of 76, found that participants who were given the fatty acids regime were significantly less likely to develop psychosis than the control [RR 0.13 95% CI 0.02 to 1.0 NNT 6 95% CI 5 to 96].

Antipsychotics and CBT
One trial, McGorry et al. (2002), intervened with an antipsychotic, (risperidone), CBT and a specialised team. The control group was supported by the specialised team. This initiative was developed with the aim of preventing transition to psychosis. No participants were lost to follow up and the sample size was 59.

Participants in the intervention group were significantly less likely to have developed psychosis at the six month follow up than controls [RR 0.27 95% CI 0.1 to 0.9 NNT 4 CI 2 to 20], however, this was not maintained at 12 months [RR 0.54 95% CI 0.2 to 1.3]. For the other outcomes, global state, mental state and quality of life, there were no significant differences between the two groups at six and 12 months, although Marshall and Rathbone (2011) note that the data was skewed and the confidence intervals were wide.

12.7.5 Summary of Interventions for Prevention of Transition to Psychosis
All of these trials were small scale, and so would need to be replicated to support greater confidence in the findings. The results suggest that E-EPA oil, the anti-psychotic, amisulpride, and a combination of anti-psychotics and CBT are strategies that warrant further investigation.

12.8 Types of Delay

12.8.1 System Delay
There is some suggestion that the type of first contact can have a bearing on the length of untreated psychosis. Patients who seek help from non physicians may wait longer for attention, but some studies have suggested that psychiatrists and psychologists may also delay referral.

12.9 Discussion

The seven reviews present outcomes of delayed diagnosis of psychosis, some determinants of delay and evaluations of early intervention services. Prevalence appears difficult to estimate because of the variation in how DUP is defined and measured.

Longer DUP is implicated in a number of outcomes which suggest a poorer prognosis for patients, including severity of symptoms after treatment, poorer social functioning and reduced rates of remission. While we failed to identify data regarding cost implications in the included systematic reviews, evidence from a UK economic evaluation suggests that early intervention is associated with substantially reduced costs due to lost employment, reduced costs attributable to homicide, savings in suicide costs and savings where an assumption of reduced re-admission rates is made (McCrone et al. 2010).

The reviews do not tell us where in the diagnostic process delay is most likely to occur, but primary research conducted by Brunet et al. (2007) in the UK indicated that the median delay within secondary services was over seven times the delay in the referral pathway, with a mean delay in mental health services accounting for 35% of overall DUP. Data from Anderson et al. (2010) suggests that those from ethnic minorities are more likely to experience a pathway into care that involves emergency services or an element of compulsion. Nevertheless, a UK study (Morgan et al. 2006) found no evidence that African-Caribbean or Black African patients experienced longer periods of untreated psychosis than White British patients prior to first contact with services.

Results from the four studies investigating multi-focus public awareness campaigns to reduce DUP are equivocal. Doctor education appears to improve the pathway into care, with more patients being referred to mental health services, more quickly.

Evaluations of strategies to inform doctors, teachers, parents and others about psychosis and the importance of early treatment showed improvements to the care pathway and to the severity of symptoms at hospital admission. There is good evidence that EIS improve outcomes for those with FEP, but larger trials may be needed. Pertinent evidence may be supplied by a full-scale RCT (Recovery After an Initial Schizophrenia Episode - RAISE), comparing two different ways of providing early treatment to people experiencing the early stages of schizophrenic disorders. As part of the RAISE trial, patients are currently being recruited at 34 study locations throughout the US to evaluate EIS including personalized medication treatment, individual resiliency training, supportive services, family psycho-education and education/ employment assistance (National Institute for Mental Health, *ongoing*).

Maintaining gains is a critical issue within the treatment of psychosis and few trials showed gains preserved beyond the treatment period - it may be that EIS is only effective while interventions are active (Birchwood and Fiorillo 2000). Research currently being conducted in the UK, the SuperEDEN (Sustaining Positive

Engagement and Recovery) project, is following up a cohort of patients to examine outcomes after being discharged from services (UK Clinical Research Network, 2012).

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13. Stroke

Stroke, like acute myocardial infarction, is a medical emergency that must be treated quickly to improve survival or reduce the risk of dependency. Patients who are treated within 3 hours of onset with thrombolysis therapy reduce their risk of death or severe disability by up to 16% (Wardlaw et al. 2003). However many patients are seen too late to benefit from treatment and often this is due to a lack of knowledge on the part of both the public and professionals (NAO 2005).

13.1 Overall summary of findings

A lack of awareness of the warning signs of stroke or transient ischaemic attacks (TIA) leads to delays in seeking help by sufferers or witnesses. This lack of knowledge is seen at the same levels for stroke patients or those at risk of stroke as the general public.

Inappropriate action, as well as lack of recognition of symptoms, contributes to delays to hospital arrival, with the majority of patients phoning their GP rather than an ambulance.

Public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services.

Multi component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy.

There was no information about outcomes and the cost implications of late diagnosis.

13.2 Included Studies

We found four systematic reviews focusing on stroke (Jones et al. 2010, Kwan et al. 2004, Lecouturier et al 2010a/b). Jones et al. (2010) examined the literature that explored the knowledge of the public, patients and relatives regarding risk factors, symptoms, treatment and sources of information about stroke and transient ischaemic attack (TIA). Although there does not seem to be a direct link to late diagnosis, lack of knowledge of the illness may contribute to determinants of delay, so this review was included.

Kwan et al. (2004) reported on evaluations of interventions that could speed up admission to hospital and administration of thrombolytic therapy.

In a review similar to Jones and colleagues, Lecouturier et al. (2010a) assessed studies investigating awareness of and response to symptoms of acute stroke or TIA, and beliefs and attitudes about diagnosis, early treatment and consequences of acute stroke or TIA. In a companion review (Lecouturier et al. 2010b), they

examined studies of mass media interventions aimed at improving emergency response to stroke. Details of the reviews are presented in table 13.1.

Number of contributing reviews: 4

Table 13.1: Characteristics of Included Studies

Study [AMSTAR score]	No. of included studies	Pooled no. of participants	Countries	Characteristics of participants	Disease state / condition
Jones et al. 2010 [9/11]	39	~141000	UK (4) Europe (8) North America (20) Asia (6) Australia (1)	General public, stroke patients, people at risk of stroke, relatives of non stroke patients.	Stoke or TIA
Kwan et al. (2004) [7/11]*	10	>6345	US (6) Canada (2) UK (1) Germany (1)	Not reported	Acute ischaemic stroke
Lecouturier et al. (2010a) [9/11]*	11	4165	UK	Stroke patients; TIA patients; at risk patients; general public; Minor stroke patients; stroke witnesses	Not reported
Lecouturier et al. (2010b) [8/11]	10	18,733	US (7) Canada (2) Germany (1)	General public aged 18 and over	Not reported
Those studies marked with an asterix satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool.					

Eleven studies overlapped: four studies appeared in Jones et al. (2010) and Lecouturier et al (2010a); three in Kwan et al. (2004) and Lecouturier et al. (2010b); and four in Jones et al. (2010) and Lecouturier et al. (2010b).

13.3 Prevalence

There was a small amount of information from the UK about extent of delay in help seeking by stroke patients and witnesses in Lecouturier et al (2010a). Two studies reported that the median delay in phoning for an ambulance or a general practitioner was 15-30 minutes and 79% sought help within an hour. In another study, 59% of patients waited to see if their symptoms resolved spontaneously as

compared to 25% of witnesses who waited. A further study showed that 44% of TIA patients did not seek medical attention for 24 hours.

13.4 Determinants

Two reviews presented information (see table 13.2) on determinants of delay (Jones et al. 2010, Lecouturier et al. 2010). Both studies concentrated on understanding patient delay, with Jones and colleagues, in particular, focusing on the contribution of knowledge about the risks and symptoms of stroke to the decision to seek help, and thus lengthening or reducing delay. As many of the findings imply delay but do not directly measure it, the number of studies with these findings are given in brackets, but not whether the results show an increase in delay (+) or a reduction (-). Those findings where there is a more direct relationship, the direction of effect is indicated.

Table 13.2 Determinants of Delay

Determinant	Jones et al. (2010)	Lecouturier et al. (2010)
Demographic		For TIA: no relationship between help seeking and age and sex (1).
Medical		Type of symptom (1-) Additional symptom of altered consciousness arrived in hospital a median of 1.5 hours (versus for those vomiting 4 hours; for seizures 4.4 hours; and headache 2.3 hours.) For TIA patients (1-) Patients with motor symptoms or symptoms lasting for more than 60 mins more likely to take emergency action. No relationship between patient delay and vascular territory of TIA or vascular risk factors, including previous stroke (1).
System		Use of ambulance (2-) Arrival in hospital for those who used emergency services: median from onset – 2 hours, 3 mins. Arrival in hospital for those who were referred by their GP: median from onset – 7 hours, 12 mins. (OR: 0.45, 95% CI 0.23 to 0.61) Access

Determinant	Jones et al. (2010)	Lecouturier et al. (2010)
		Timing of onset (1+) Onset between midnight and 6 am delays greater than 6 hours between onset and arrival at hospital (OR 1.22, 95% CI 1.04 to 1.45) TIA patients delayed seeking help if onset occurred out of GP practice hours, particularly an issue at weekends. (1+)
Patients' knowledge, attitudes and beliefs	Demographic People less able to identify risk factors Age (3) - older people (>65 years (1), >75 years (1)) Older stroke patients and those at risk (1) Ethnicity (2) African Americans SES (4) Lower levels of education People with less knowledge about symptoms Age (3) – older people (>/=65 years and >/=70 years (1), > 75 years (1)) Older stroke patients and those at risk (1) Ethnicity African Americans (3) Hispanics (1) Patients and those at risk Knowledge range similar to general public (2) Older age associated with decreased likelihood to call emergency services (1+). Action More people were likely to take action if experiencing weakness / paralysis (42%) compared with dizziness (2%) (1-)	Demographic Age Younger people were more able to identify symptoms (2) Greater knowledge was not associated with age, gender or family history of stroke (1) 61% of patients and 80% of witnesses were concerned about bothering other people (1+) Recognition of symptoms of TIA did not influence whether or not patients sought immediate medical assistance or presentation time at hospital (2) Less than half of patients recognised that they were having a stroke (2) or TIA (1). TIA patients with motor symptoms more likely to correctly interpret symptoms than those without (49% vs 36% p=0.046), as were those with previous TIA (58% vs 40% p=0.044) (1) Witnesses were more likely to consider symptoms as serious (1) A majority of patients at risk of a stroke and members of the public considered stroke as always an emergency (2).

Determinant	Jones et al. (2010)	Lecouturier et al. (2010)
	Between 27% and 100% of participants stated that they would call an ambulance if they suspected a stroke (3), but of patients who had suffered a stroke, 18% had called the emergency services, and 80% had called their GP (1). TIA Term TIA unfamiliar to 87% of participants (1) 8% recognised TIA as a symptom of stroke resolving within 24 hours(1) 3% recognised TIA as a disease that needed immediate medical attention (1) 8% identified the correct definition of TIA (1) 9% identified a typical symptom (1)	
Other		Onset not at home reduced delays (p<0.0001) (1-)

Key Determinants of Delay

Medical

- The type of symptom experienced by stroke sufferers, i.e. altered consciousness, and TIA patients, i.e. motor symptoms or those lasting more than an hour, prompted earlier calls for assistance.

System

- Use of emergency services by patients reduced delay as compared to those patients referred by a GP.
- Delays were more likely for those with onset outside of GP hours (TIA) or at night (stroke).

Patients' knowledge, attitudes and beliefs

- There was some evidence to suggest that older people and ethnic minorities knew less about the risk factors and symptoms of stroke. Stroke patients and those at risk of stroke had levels of knowledge that were similar to the general public.

- Having some knowledge of stroke did not seem to lead to prompt action when a patient was suffering a stroke, and most people consulted a GP rather than calling an ambulance, even though the stated intention was to use the emergency services.

- There was even less knowledge of TIA, with 87% of respondents in one study saying they were not familiar with the term.

- There was a reluctance to bother other people by patients and witnesses.

Other

- When onset occurred at home, there were longer delays.

13.5 Outcomes

There is no information about the outcomes of late diagnosis of stroke.

13.6 Cost Implications

There is no information about the cost implications of late diagnosis of stroke.

13.7 Interventions

Three studies investigated interventions to improve treatment delay of stroke. Jones et al. (2010) and Lecouturier et al. (2010b) concentrated on public awareness campaigns to improve knowledge of stroke symptoms. Additionally, Lecouturier and colleagues reported on interventions to educate health professionals, such as paramedical and emergency department staff, on the signs of stroke. Kwan et al. (2004) examined interventions to improve the efficiency of delivery of thrombolysis for acute stroke. This review included public education campaigns but interventions were multi component and included training strategies directed at medical staff and re-organisation of hospital routines.

Seven studies, evaluating public education campaigns and included in Jones et al. (2010) and Lecouturier et al. (2010), had outcomes reported by the reviews. Jones and colleagues found nine reports but only discussed three in enough detail. All of these were before and after studies, and two had control groups (Silver et al. Fogle et al. 2010). Details of the results are presented in table 13.3.

The public education campaigns included advertisements on television, radio and in newspapers. Articles and interest stories were printed and information leaflets and flyers distributed to doctors, pharmacies and community groups. The outcomes measured were: the ability of the public to recognise symptoms or warning signs of

a stroke (measured by all seven studies), and to act on these signs by seeking urgent help (measured by five studies). One study (Silver et al. 2003) differentiated between the methods used in the campaigns and was able to show the relative effectiveness of television compared to print media.

All seven studies were able to report a significant increase in the knowledge of symptoms among the public. However the awareness of the need for an emergency response rose slightly in three studies and decreased in one. Hodgson et al. reported a significant rise in the number of visits to the emergency department, although the proportion of patients arriving at hospital between 2.5 and 5 hours did not change during the campaign. Both studies conducted by Fogle and colleagues (2008 and 2010) were able to show an increase in the number of people who would call the emergency services if they experienced or witnessed particular symptoms.

Table 13.3: Outcomes from Public Awareness interventions

Study (Design)	Description of intervention	Recognition of symptoms	Need to seek urgent help
Hodgson et al (Before and after study)	Newspaper and TV advertising	↑% of population able to name two or more warning signs 52.1% to 72.3% (p<0.001) (6 months later dropped to 63.9%) ↑Mean no. of warning signs 1.69 to 2.31 (p<0.001) (6 months later dropped to 1.99)	↑significant increase in visits to the ED. Proportion arriving in hospital within 5 and 2.5 hours not affected during campaign.
Silver et al (Controlled before and after study)	High intensity TV information campaigns Low intensity TV campaigns Print (newspapers) High Intensity TV Low intensity TV Print	↑% of population able to name two or more symptoms 40.4% to 54.1% (p<0.001) ↑% of population able to name two or more symptoms 38.8% to 49.5% (p=0.002) % of population able to name two or more symptoms 41.7% to 40.8% (p=0.8) Control group = 43.7% to 35.9% (p=0.022) ↑Mean no. of warning signs 1.69 to 2.31 (p<0.001) 1.27 to 1.47 (p=0.021) 1.25 to 1.17 (p=0.280) Control group = 1.38 to 1.10 (p=0.001)	
Stern et al. (Before and after study)	Community slide / audio education programme	↑Mean pre and post test scores from 69% to 79%	

Study (Design)	Description of intervention	Recognition of symptoms	Need to seek urgent help
Becker et al. (Before and after study)	TV and newspapers information campaigns Stroke interest stories in community publications, translated into 5 languages. Public screenings for ethnic groups Distribution of flyers	↑Awareness of >/= stroke symptom 7% point increase (p=0.032)	Awareness of emergency response 4% point decrease (ns)
Marx et al. (Before and after study)	Poster advertisements, flyers, mail circulars, slogans, interest stories in local newspapers, on TV and radio, and public events	↑% of population correctly identifying 'paresis / weakness' as a symptom 88% to 95% (p<0.01) ↑% of population correctly identifying that stroke can occur 'at any age' 45% to 62% (p<0.005)	Awareness of emergency response 81% to 82% (ns)
Fogle et al .2008 (Before and after study)	TV and radio advertisments. Newspaper ads placed in local paper every Sunday during intervention	↑% of population able to name two or more warning signs 67% to 84% (p<0.05) ↑mean number of warning signs 1.82 to 2.25 (p<0.05)	Awareness of emergency response 2% increase (ns) Would call 911 if experienced: ↑Paralysis – 42% to 58% (p</= 0.05) ↑Numbness – 41% to 51% (p</=0.05) ↑Speech problems – 51% to 58% (p</=0.05)
Fogle et al. 2010 (Controlled before and after study)	Same as above and in addition educational material sent to physicians, pharmacies, churches and care homes. Informational brochure and fridge magnet sent to households in target groups.	↑% of population able to name two or more warning signs 73% to 82% (p<0.05)	Awareness of emergency response 3% increase (ns) Would call 911 if experienced: ↑Any of the three symptoms 9% increase – 39% to 48% (p</=0.05) No significant change in control community

↑= statistically significant increase; ↓= statistically significant decrease

Eleven studies evaluated multi-component programmes which included public and professional education, helicopter transfer for suspected stroke patients, establishment of acute stroke teams, and training for staff in the administration of recombinant tissue plasminogen activator (rt-PA). These were examined in two reviews (Lecouturier et al. 2010b and Kwan et al. 2004). None of these studies were randomised controlled trials, but one was a quasi experimental study with control hospitals matched with the intervention centres, and one was a comparison study. There were four uncontrolled before and after study designs and five observational studies. Details of the results are presented in table 13.4.

The measured outcomes related more directly to time to treatment and included: time to arrival in hospital (eight studies); use of ambulance or helicopter transfer (two studies); received recombinant tissue plasminogen activator (rt-PA) (seven studies); in hospital delays (four studies); and percentage of correct diagnosis by paramedics (two studies).

Of the eight studies (Alberts et al. 1992, Barsan et al. 1994, Morgenstern et al. 2002, Behrens et al. 2002, Harbison et al. 1999, Gomez et al. 1994, Hill et al. 2000, Wojner Alexandrov et al. 2005) examining time to arrival in hospital, four could show a significant decrease in delay, one showed a decrease but it was not significant, and two found no significant difference. One observational study reported the median delay as 1.2 hours but the review did not report a comparison.

Two studies (Barsan et al. 1994, Silliman et al. 2003) reported on use of ambulance services or helicopters to transfer patients to hospital. One reported an increase in use of ambulances during the intervention, and one reported on the number of patients transferred by helicopter and the percentage of those arriving within 3 hours. Silliman et al. 2003 calculated the average cost of a helicopter transfer: $4623. They did not carry out a cost-effectiveness analysis but remarked that increased cost of helicopter use could be offset by potential savings in rehabilitation and nursing home expenses, that would be associated with a delay in treatment.

Increases in rates of administration of thrombolysis, most often with rt-PA, were seen in three studies (Morgenstern et al. 2002, Behrens et al. 2002, Wojner Alexandrov et al. 2005); in one study the increase was significant. The four other studies reported the percentage of patients that received the treatment, but the review did not report a comparison (Hill et al. 2000, Riopelle et al. 2001, Silliman et al. 2003, Barsan et al. 1994).

All of the four interventions reporting on in-hospital delay, described improvements in time from arrival or onset of symptoms to first medical assessment, CT scanning, neurologist assessment and start of thrombolysis (Behrens et al. 2002, Gomez et al. 1994, Englander et al. 1998, Hill et al. 2000) . Only one study did not report a significant reduction. Both of the studies evaluating the ability of paramedics to make accurate diagnosis of stroke, showed correct diagnosis in 83% and 79% of cases, the second study showing an 18% point increase after the intervention (Harbison et al. 1999, Wojner Alexandrov et al. 2005).

Overall, public awareness campaigns have been shown to have some impact on knowledge, but less on awareness about the need for an emergency response. Only two of the studies had control groups which must weaken the confidence in the evidence for public awareness campaigns. For the multi-component studies, there was evidence of a reduction in patient delay, in delay during triage and in-hospital delays, leading to an increase in timely and appropriate administration of thrombolysis for a greater number of patients. Only one of these studies was quasi experimental with a matched control group and one other study compared outcomes for patients in the intervention group with those who received standard care. Kwan and colleagues suggest that multi component interventions hold the greatest possibilities for making a consistent difference. However Lecouturier and colleagues argued that, due to the evaluations' design, it was impossible to differentiate between the different components of the intervention to make a judgement about what affected delay most, be it the impact of education on patient decision time or the impact of training on professional expertise of medical staff in recognising stroke in its early stages.

Table 13.4: Outcomes from public and professional education interventions

Study (Design)	Description of intervention	Time to arrival in hospital	Use of ambulance or helicopter transfer	Received thrombolysis (rt-PA)	In hospital delays	Correct diagnosis by paramedics
Alberts et al. 1992 (Before and after study)	Educational intervention for public, primary care physicians and ED staff. Supplemented by use of helicopters for rapid transfer to specialist centres.	Time ↓ Proportion of patients arriving within 24 hours of onset increased from 37% to 86% (p=0.0001)				
Barsan et al.1994 (Observational)	Educational programme for public, paramedical staff and ED staff.	Median delay reduced from 3.2 to 1.5 hours (p<0.32)	↑ ambulance use rose from 39% in first quartile to 60% in fourth quartile	3.5% of patients		
Morgenstern et al. 2002 (Quasi-experimental control not randomly selected, but matched hospitals and demography)	Educational programme for the public and ED staff; public also encouraged to be 'assertive in asking the physician about rt-PA	Arriving within 2 hours of symptom onset not significant		↑For intervention group, ischaemic stroke only 6.44% increase from 2.44% to 8.65% (p=0.02) rising further to 11.2% 6 months later. Eligible patients 38% increase, rising from 14% to 52% (p=0.003), rising further to 69%, 6 months later. Control parallel group no significant difference		

Study (Design)	Description of intervention	Time to arrival in hospital	Use of ambulance or helicopter transfer	Received thrombolysis (rt-PA)	In hospital delays	Correct diagnosis by paramedics
Behrens et al. 2002 (Before and after study)	Training programme for paramedical and ED staff. Trained in a) clinical assessment of patients with suspected stroke and the need to transfer them immediately to hospital; b) rapid triage of stroke patients in ED, resulting in urgent CT scanning and administration of rt-RA or other forms of therapy.	↓mean delay from symptom onset to hospital arrival (5.2 to 3.3 hours) ↓Time. Significant increase in the proportion of patients arriving within 3 hours – 2% to 15%.		↑proportion receiving rt-PA – from 2% to 11%.	↓mean delay from diagnosis to start of therapy (2.6 to 1.6 hours)	
Harbison et al. 1999 (Observational)	Training programme for paramedical staff to improve the accuracy of stroke diagnosis and speed up transfer to hospital.	Median delay from symptom onset to hospital arrival was 1.2 hours				Correct diagnosis by paramedics of stroke or TIA in 83% of patients.
Silliman et al. 2003 (Observational)	Training programme for paramedical staff about the use of rt-PA in patients with acute stroke. Supplemented by helicopter transfer to specialist centre.		111 patients with suspected stroke transferred by helicopter, 71% arrived within 3 hours	21% of those arriving within 3 hours received rt-PA		

Study (Design)	Description of intervention	Time to arrival in hospital	Use of ambulance or helicopter transfer	Received thrombolysis (rt-PA)	In hospital delays	Correct diagnosis by paramedics
Gomez et al. 1994 (Non-randomised clinical study)	Implemented a 'code stroke' protocol, which used centralised pager system to alert all members of acute stroke team when patient with suspected stroke arrived in ED.	No significant difference in delays from symptom onset to hospital arrival.			↓reduced delay from arrival to first medical assessment from 101 to 46 minutes. No significant difference in delays from first medical assessment to start of therapy.	
Englander et al. 1998 (Before and after study)	Implemented a continuous quality improvement scheme which involved new algorithms and evaluation forms for assessing patients presenting with acute stroke.				↓delay from hospital arrival to first medical assessment (45 min. to 10 min.) ↓delay from hospital arrival to CT scanning (117 to 46 mins.) ↓delay from hospital arrival to neurologist assessment (76 to 46 mins.)	

Study (Design)	Description of intervention	Time to arrival in hospital	Use of ambulance or helicopter transfer	Received thrombolysis (rt-PA)	In hospital delays	Correct diagnosis by paramedics
Riopelle et al. 2001 (Observational study)	Evaluated a Regional Acute Stroke Protocol containing 3 elements: a) training for paramedical staff; b) training of ED staff including transfer of patients to nearby tertiary centre for thromoblysis; c) development of acute stroke activation system at regional centre, involving aterting the acute stroke team, immediate CT scanning and administration of rt-PA			22% received rt-PA (42 of 191 patients)		

Study (Design)	Description of intervention	Time to arrival in hospital	Use of ambulance or helicopter transfer	Received thrombolysis (rt-PA)	In hospital delays	Correct diagnosis by paramedics
Hill et al. 2000 (Observational study).	Evaluated a multifaceted programme including: a) education of public; b) training of paramedical and ED staff; co development of the acute stroke team; d) training of staff working the neuro-observation unit on how to administer rt-PA; e) development of daily TIA clinic.	↓mean delay from symptom onset to hospital arrival (63 to 49 min)		2.6% of 1127 patients received rt-PA	↓delay from symptom onset to CT scanning (113 to 90 min). ↓delay from symptom onset to start of rt-PA (168 to 147 mins).	
Wojner Alexandrov et al. 2005 (Before and after study)	Multi media public education about the warning signs of stroke; education sessions for paramedics and hospital staff with comparative benchmarking of hospital and paramedic performance; implementation of the Los Angeles Pre-Hospital Stroke Scale by the fire department	↓Time Arriving within 2 hours of symptom onset 4% increase – 58% to 62% (p=0.002)		Thrombolysis rates in 4 centres % point increases of: 3.9, 6.8, 8.1 and 12.5. In 2 centres decreases of 3.6% and 6%		↑18% increase of positive predictive value from 61% to 79%

↑= statistically significant increase; ↓= statistically significant decrease

13.8 Types of Delay

13.8.1 Patient Delay
Lack of knowledge of stroke or TIA symptoms and the need to call an ambulance were major determinants of delay. This was found equally in previous stroke patients, people at risk of stroke and the general public.

13.8.2 System Delay
Delays to treatment were more likely if symptom onset was at night or at the weekend.

13.9 Discussion

Three of the four reviews in this section concentrated on studies that described patient delay and its relationship with knowledge of the symptoms and warning signs of stroke. Only one, Kwan et al. (2004), reviewed research that reported on interventions to overcome treatment delays, whether arising from patient, doctor or system barriers. These interventions covered public education, training of professionals or implementing changes to routines in order to improve the speed of administration of thrombolysis.

Unsurprisingly, the reviews (Jones et al.2010, Lecouturier et al. 2010) found that lack of knowledge of the warning signs of a stroke or a TIA, as well as lack of action needed when a stroke is suspected, were major determinants of delay. When and where the onset of the stroke took place also impacted on delays in help seeking, with longer intervals occurring if onset started at night, at the weekend or at home. Information about delays in Lecouturier et al. (2010a) is particularly useful as they gathered evidence from the UK only.

The outcomes measured by the different interventions varied, with improvements in the knowledge of symptoms perhaps the least direct measure of reductions in delay. Of more obvious utility were reductions in time to arrival at hospital, the shortening of the assessment period before treatment, and the use of the emergency services for transfer to hospital.

None of the evaluations were randomised controlled trials, which, as Kwan et al. (2004) acknowledged, are difficult to execute for interventions designed to improve the efficiency of emergency services. Lecouturier et al. (2010b) expressed disappointment in the quality of the studies and considered the evidence as weak because it was based mainly on uncontrolled before and after studies. Nevertheless, the evidence from these interventions suggests that multi component strategies can be effective in improving the time from onset to the administration of rt-PA. However, such strategies can be expensive and difficult to implement, and so both reviews called for more robust evaluation and cost-effectiveness research to be commissioned for interventions to reduce treatment delay in stroke.

Recently, the Department of Health instigated a major 3 year communications campaign, *the FAST test:* Facial weakness, Arm weakness, Speech difficulties and Time to act fast, which commenced on 7th February 2009 with the objective of enabling members of the public to recognise and identify the main symptoms of

stroke and know that it needs to be treated as an emergency. The campaign used mass media including television, print, radio and the internet (Department of Health, 2009). An evaluation of the FAST campaign suggested that it performed well in terms of spontaneous and prompted recognition of the symptoms of stroke but that knowledge was highest following the second of five waves of the campaign, when spend was highest (TNS BMRB, 2010). Following the most recent advertising campaign in March 12, an independent tracking survey among over 1800 adults, carried out by TNS BMRB, showed that the campaign was successful in increasing knowledge of stroke symptoms (any symptom:98%) and in improving awareness of the need to access services to the highest level seen so far at 74%. Higher scores were achieved by those aware of the FAST campaign and improvements were seen among key BME group also, (personal communication from Karen Pinder, Health Protection and Older People's Marketing Manager, Department of Health). An evaluation of stroke awareness campaigns conducted in England, Australia and Canada using pre- and post-campaign surveys found the greatest improvement in stroke awareness was created by the multifaceted FAST campaign, which had the greatest budget and reach (Trobbiani et al. *in press*).

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14. Tuberculosis

Tuberculosis (TB) is an infectious disease where late diagnosis will affect the extent of transmission to other people. Many of the papers within the included systematic reviews were concerned with time delays, and two reviews focused specifically on the length of time from first symptom to confirmed diagnosis (Sreeramareddy et al.2009, Storla et al. 2005). We present findings of this kind of delay under prevalence. The findings of the systematic reviews are presented in sections 14.1 to 14.8 immediately below.

The primary studies within the included systematic reviews often examined populations outside of the UK. While informative, the reviews had limited relevance to the UK healthcare system. Therefore, the findings of 12 UK primary studies examining delayed diagnosis for TB are presented after the findings of the systematic reviews in section 14.9 to 14.18.

14.1 Overall Summary of Findings (Systematic Reviews)

> *Statistically, there was no difference in time delays in low or high endemic countries, or low, middle, or high income countries.*
>
> *The type of health care site and/or health practitioner that is initially accessed by patients seems to impact on the speed of diagnosis. Poverty, rural residence, being a woman, low awareness of tuberculosis and older age are associated with a greater risk of late diagnosis.*
>
> *There was no information about the outcomes or cost implications of late diagnosis of tuberculosis within the included reviews.*
>
> *There may be some merit in reminder systems to encourage return for results of tests, but more robust trials are needed.*

14.2 Included Studies

There were four reviews examining late diagnosis and tuberculosis (Courtwright and Turner 2010, Liu et al. 2008, Sreermareddy et al 2009, Storla et al. 2008).

Courtwright and Turner (2010) reviewed the literature on TB stigma to identify the causes and evaluate the impact of stigma on TB diagnosis and treatment. Only 38 of 99 articles identified looked at the effect of stigma on the diagnosis and treatment of TB, of which 19 discussed the effect of stigma upon diagnosis. Only the 19 studies pertaining to diagnosis are included within this review.

Liu et al. (2008) assessed the effects of reminder systems and late patient tracers on completion of diagnostics, commencement of treatment in people referred for curative or prophylactic treatment of tuberculosis, completion of treatment in people starting curative or prophylactic treatment for tuberculosis, and cure in people being treated for active tuberculosis. Five of the nine included studies were relevant for this review.

Sreeramareddy et al. (2009) summarized the data on delays in the diagnosis of TB. Storla et al. (2005) also examined time delays for diagnosis and treatment and in addition, identified determinants of delay.

The characteristics of the included reviews examining delayed diagnosis of tuberculosis are presented in Table 14.1.

There was considerable overlap of primary studies between two reviews. Thirty studies were common to both Storla et al. (2008) and Sreeramareddy et al. (2009). Two studies from Courtwright and Turner (2010) also appeared in these two other reviews. Full details of the primary studies common to more than one review can be found in Table A5.2 in Appendix 5.

No. of contributing reviews: 4

Table 14.1: Characteristics of the included reviews examining delayed diagnosis of tuberculosis.

Study [AMSTAR score]	No. of included studies	No. of pooled participants	Countries	Characteristics of participants	Disease state / condition
Courtwright and Turner 2010 [5/11]	99 studies of which 19 were relevant	Not reported	Asia/Pacific Islands (33%); Africa/Middle East (28%); Multiregional (17%); North America (9%); Latin/South America (8%); Europe/ Russia (4%)	Not reported	Not specified
Liu et al. 2008* [10/11]	9 studies of which 5 were relevant	4,089 for diagnosis studies	US	Children and adults in any setting referred (including self-referred) to tuberculosis diagnostic or screening services.	Pulmonary tuberculosis (diagnosed by sputum microscopy, culture, or both, regardless of HIV status), smear-negative pulmonary tuberculosis (diagnosed by symptoms and chest radiograph findings or other diagnostic tests, regardless of HIV status), or extra-pulmonary tuberculosis (diagnosed by signs or symptoms and histopathology, sputum acid-fast bacilli smear, culture, or both, imaging studies or polymerase chain reaction (PCR)).

Study [AMSTAR score]	No. of included studies	No. of pooled participants	Countries	Characteristics of participants	Disease state / condition
Sreeramareddy et al. 2009* [10/11]	52	Not reported	China (5) India (3) Malaysia (3) Turkey (3) Vietnam (3) Ethiopia (2) Pakistan (2) South Africa (2) Syria (2) Thailand (2) US (2) Argentina (1) Australia (1) Bangladesh (1) Bolivia (1) Botswana (1) Columbia (1) Egypt (1) Gambia (1) Ghana (1) Hong Kong (1) Iran (1) Iraq (1) Italy (1) Japan (1) Kenya (1) Korea (1) Mongolia (1) Nepal (1) Norway (1) Somalia (1)	Not reported//	Studies included which had reported the patient, health system and total delay in the diagnosis of pulmonary tuberculosis made by either sputum/culture positivity. Studies excluded which described extra-pulmonary tuberculosis only.

Study [AMSTAR score]	No. of included studies	No. of pooled participants	Countries	Characteristics of participants	Disease state / condition
			Taiwan(1) Tanzania (1) UK (1) Yemen(1)		
Storla et al. 2008 [5/11]	58	Not reported	Thailand (4) China (3) Ethiopia (3) United States (3) Australia (2) Iran (2) Japan (2) Malawi (2) Malaysia (2) Botswana Pakistan (2) Spain (2) Turkey (2) UK(2) Burkina Faso(1) Cambodia (1) Egypt (1) France (1) Gambia (1) Ghana(1) India (1) Iraq (1) Italy (1) Korea (1) Mongolia (1) Nepal (1) New Zealand (1) Nigeria (1)	Some studies excluded visitors, mortal cases, and individuals with mental disturbances. The age-related exclusion criteria also varied: most studies excluded cases below the age of 16 years, some excluded cases below the age of 18 years, and a few included children of all ages. One study did not include patients who had undergone 2 or more months of treatment.	17 studies included all new TB cases, 11 included all pulmonary TB cases, 3 included all cases with a positive sputum smear, 24 included all new cases with a positive sputum spear, 3 studies data not obtainable. Some studies carefully excluded all cases with chronic underlying pulmonary conditions that could interfere with the patient's definition of symptom onset, but most did not.

Study [AMSTAR score]	No. of included studies	No. of pooled participants	Countries	Characteristics of participants	Disease state / condition
			Norway (1) Peru (1) Romania (1) Somalia (1) South Africa (1) Syria (1) Taiwan (1) Tanzania (1) Uganda (1) Vietnam (1) Yemen (1) Zambia(1)		
These reviews satisfied criteria 3, 6 and 7 of the AMSTAR quality assessment tool (see Appendix 2).					

14.3 Prevalence

There were two reviews which contributed to our understanding about prevalence, Sreeramareddy et al. (2009) and Storla et al. (2005).

Sreeramareddy et al. (2009) focused on patient and health system delay in low and middle income countries (LMIC) and high income countries (HIC), for patients suffering from pulmonary TB. They excluded studies that described extra-pulmonary diagnosis.

Table 14.2: Median average and range of days for diagnosis of TB (Sreermareddy et al. 2009)

	Patient Delay (median/range)	Health System Delay (median / range)	Overall Delay (median /range)
LMIC	31.7 days/4.9 to 162 days	28.4 days/2 to 87 days	67.8 days /25 to 185 days
HIC	25.8 days/7 to 34.5 days	21.5 days/7.2 to 36 days	61.3 days/42 to 89 days
Statistical significance of difference between LMIC and HIC delay (p-value)	0.637	0.684	0.204

The overall average patient delay was similar to health system delay (31.03 versus **27.2 days). This was not different when analysed separately for LMICs and HICs (p**= 0.506). None of the types of delay, patient, health system or overall, were statistically different between LMICs and HICs. A full breakdown of the extent of patient delay and health system delay is displayed in table 14.2.

Similarly, Storla and colleagues found that most of the studies, whether they looked at low or high endemic countries, reported a total delay within a range of 60-90 days (mean ± SD: 72 days ± 28 days).

In the Sreeramareddy et al. (2009) review, it is important to note that the UK was ranked the second highest in terms of delay after the United States, at a total of 78 days (34.5 patient delay days and 29.5 health system delay days) in the HIC group. This information was taken from a retrospective study, conducted in 2001-2, of 70 TB patients (Paynter et al. 2004), living in the catchment area of a North London hospital.

Likewise, Storla et al. (2008) ranked all the countries in its 58 studies in terms of overall delay. One study, conducted in London, (Lewis et al. 2003) found an overall

delay of a median average of 126 days, putting the UK second highest in the table of all countries, both high income and lower and middle income. However, a second London study, (Rodger et al. 2003) found the median delay was 49 days, placing the UK 46th in the table. Lewis et al. (2003) looked at 93 patient records in East London, and Rodger et al. (2003) analysed surveillance data from 1998 to 2000 for 853 patients to calculate the median average delay.

Storla and colleagues found there was no consistent pattern regarding the relative contributions of patients and healthcare providers to the diagnostic delay. Patient related delay was seen in studies in London (Lewis et al.), Romania, Vietnam, Nigeria, South Africa, Australia (Queensland), Ethiopia (Addis Ababa), Korea, Somalia, Syria, Turkey (Istanbul), Japan (Chiba), Iraq, USA (New York), Yemen, and China (Shanghai). Healthcare systems as the main cause of delay was identified in the studies of Tanzania, Ghana, Pakistan, Malaysia, Iran (WHO, nationwide), Botswana, New Zealand, Uganda, Ethiopia (Amhara), Italy, and China (Jianhu). Twelve studies reported an almost equal contribution of patients and healthcare system to the overall delay and the remaining studies did not record the relative importance of these two factors in the delay.

14.4 Determinants

Two reviews contribute to our understanding of the determinants of delay, Courtwright and Turner (2010) and Storla et al. (2008). Courtwright and Turner focus specifically on the contribution of stigma to delay while Storla and colleagues identify a broader set of factors. Determinants of late diagnosis of tuberculosis are presented in table 14.3: the number of studies provided data for each determinant and positive (+) or negative (-) risks for delay are recorded. Neither review recorded whether or not these factors had a statistically significant association with an increased risk of delayed diagnosis.

Table 14.3: Determinants of late diagnosis of tuberculosis

Determinant	Courtwright and Turner 2010	Storla et al. 2008
Demographic	**Gender** Female (4+, 1-) **Socio-economic status** Subsistence farming (1+)	**Gender** Female (12+, 4-) **Age** Old age (12+, 2-) **Ethnicity** White (v. aboriginal) (1+); Muslim (1+); Belonging to an indigenous group (1+); **Socio-economic status** Rural residence (10+); Poverty (13+, 1-); Low educational level / awareness of TB (15+, 1-); Occupation (farmer) (1+); No health insurance (1+); History of immigration or illegal residency (7+) **Marital status/ Family structure** Married (1+); Single (2+); Large family size (1+);
Medical	Daily alcohol use (1+)	**Comorbidities** HIV (1+, 3-); Coexistence of cough or other lung disease (4+, 1-); Alcoholism and substance abuse (6+); Sexually transmitted infections (1+) **Atypical presentation** Negative sputum smear (3+, 1-); No haemoptysis (2+); Non-specific presentation (6+) leading to misdiagnosis (1+); **Less severe and indifferent symptoms (1+)** **Other** Extra-pulmonary TB (3+); Generally poor health (1+); Smoking (2+)

Determinant	Courtwright and Turner 2010	Storla et al. 2008
System		**Access** Geographical /socio-psychological barriers) (16+); Initial visit to government low level healthcare facility (10+, 1-); Initial visit to traditional healer / unqualified practitioner (10+); Initial visit to private practitioner (12+); Initial visit to tertiary services / hospital (1+, 4-); Initial visit to primary care doctor (2+)
Knowledge, beliefs and attitudes of patients	Stigma (5+,3-) as a barrier to help seeking At risk individuals report fear of TB stigma is barrier to screening (3)	Beliefs (not curable, caused by evil spirits) (3+); Stigma (1+); Self-treatment (3+)
Knowledge, beliefs and attitudes of clinicians	Stigma (5+)	

Determinants: Key Findings

Demographic

- Female gender, poverty, old age and low educational level or awareness of TB were the main risks associated with late diagnosis of TB.

Medical

- Co-morbidities, such as other lung diseases, substance abuse and alcoholism, and sexually transmitted infections, contributed to a delay in diagnosis, but there was some evidence to suggest that a HIV diagnosis promoted detection of TB.
- The early manifestations of TB meant that patients often presented with non-specific symptoms which led to misdiagnosis.
- Negative sputum smear results were mostly associated with delays, although one study showed these were not associated with risk for delay.

System

- A major cause of delay was low access to health care facilities. The type of facility that was accessed on the initial visit was important. Low level healthcare centres often had limited diagnostic facilities and poorly trained staff, and private practitioners demonstrated a low awareness of TB. If the initial visit was to a hospital or other tertiary services, delay was less likely.
- Papers reported repeated consultations with different health care providers without a correct diagnosis. Multiple visits were sometimes made to the same level of provider, and sometimes to the same physician. For example, 45% of patients received their diagnosis after a third visit in one study from Malaysia (Hooi 1994).

Knowledge, beliefs and attitudes

- Health professionals and patients agreed that stigma was an important factor in seeking a diagnosis.
- Storla et al. (2008) also found that beliefs about TB (not curable, caused by evil spirits) and self-treatment contributed to delays.

14.5 Outcomes

None of the studies had data relating to the outcomes of delayed diagnosis of tuberculosis.

14.6 Cost implications

None of the studies had data relating to the cost implications of delayed diagnosis of tuberculosis.

14.7 Interventions

One review (Liu et al. 2008) investigated the impact of reminders and late patient tracer strategies for improving the rate of diagnosis and compliance to treatment. In our review we are interested in the five studies that used these strategies to support diagnosis. (Cheng et al. 1997, Roberts 1983 (two experiments in one paper), Tanke and Leirer 1994, Tanke et al. 1997)

All of the studies were conducted in the US, and participants included children (Cheng et al. 1997), college students (Roberts 1983), and patients from a TB control programme (Tanke and Leirer 1994, Tanke et al. 1997). The outcomes of interest were failure to return for a skin test reading (Cheng et al. 1997, Roberts 1983), failure to adhere to appointments, and the number of patients that delayed their return for 2 or 3 days (Tanke and Leirer 1994, Tanke et al. 1997). The characteristics of the interventions that were studied are presented in Table 14.4.

Table 14.4: Characteristics of interventions to reduce delay diagnosis of tuberculosis

Primary study	Intervention	Control group intervention	Supplementary interventions
Cheng et al. 1997	Reminder phone call. Written information sheet with times to return. Skin tests circled in permanent marker. Date of return stamped on mother's and child's hands.	Routine verbal and written instructions.	Positive reinforcement (transportation tokens, toy on return). Negative reinforcement group (asked to leave school forms until return, told that test would be repeated if return delayed). Parents trained to read test. Nurse home-visit scheduled to verify results.
Roberts 1983i	Take home card. Postcard. Telephone call.	Direct person to person reminder.	
Roberts 1983ii	Take home card with or without enhanced message on the importance of returning, and with or without three types of overt commitment of return.	No reminder card.	

Primary study	Intervention	Control group intervention	Supplementary interventions
Tanke and Leirer 1994	Basic reminder: pre-recorded message. Basic reminder plus authority endorsement. Basic reminder plus importance statement. Basic reminder plus importance statement plus authority endorsement.	No reminder message.	
Tanke et al. 1997	Pre-recorded telephone reminder messages in the participant's primary language.	No reminder message.	

Cheng et al. (1997) found that there was a significant difference in attendance of children for Mantoux test reading when parents received a reminder phone call (RR 0.70, 95% CI 0.50 to 0.99; n=246) compared to no reminder.

In a study with 200 participants, Roberts (1983) reported no significant difference in effect between the types of return reminders from experts or non- experts, or between reminders delivered as a take home card, a post card, a telephone call, or a person-to-person message. Equally, a second experiment (n=533) showed no significant difference in attendance at clinic appointments between reminder and control groups.

Tanke and Leirer (1994) found there was no significant difference in attendance at clinics between reminder and control groups whatever the combination of messages (RR 0.94, 95% CI 0.79 to 1.12; n=857). However, Tanke et al. (1997) reported a significantly positive effect of the automated telephone call (7% failed to return) on return for the test reading compared to no reminder (12% failed to return), with an odds ratio of 1.71 (p<0.05).

Liu et al. (2008) concluded that the quality of the trials on reminders made it difficult to recommend the practice. There was emerging evidence that reminders could have some positive effects on adherence to clinic appointments but they

called for trials of higher quality to establish what kind of reminders (in which settings) were most effective, particularly in developing countries.

14.8 Types of Delay

The primary studies in these reviews were conducted in a wide range of countries with varied health systems. Surprisingly, both Sreerarameddy and colleagues, and Storla and colleagues found that the median average time for diagnosis was not statistically different between high and low endemic countries, or low, middle and high income countries. All the reviews identified delays by patients in presenting to healthcare professionals, and delays between the initial contact stage and completion of the diagnostic process. Liu et al. (2009) reviewed reminder strategies to improve completion of this process, and found that although the quality of the trials was not strong, there may be some merit in pursuing these strategies.

14.8.1 Patient Delay

There was some reluctance by patients to seek a TB diagnosis because of beliefs about the disease (Storla et al. 2005) and the stigma associated with it (Storla et al. 2005, Courtwright and Turner 2010). Lack of knowledge about the disease contributed to delay as well as the difficulty of accessing healthcare, particularly if the patient was poor and lived in the countryside.

14.8.2 System Delay

In different countries, patients can seek a diagnosis from a varied group of healthcare professionals, including healthcare workers trained to conduct TB tests at low-level government health centres, private practitioners, traditional healers and primary care physicians. Delays were reported depending on the kind of health site the patient went to initially. If patients went to a hospital on the first visit, they were most likely to get a timely diagnosis. Problems at health centres included limited access to diagnostic facilities and poorly trained staff. Private practitioners, on the other hand, were found to have a low awareness of TB. Storla and colleagues found that patients often had to make multiple visits to providers before they received the correct diagnosis.

14.9 UK primary studies examining delayed diagnosis for tuberculosis (TB)

Four systematic reviews addressing late diagnosis and tuberculosis were identified, but the preponderance of primary studies within these reviews examined populations outside of the UK. While informative, these reviews have limited relevance to the UK healthcare system. We present the findings of 12 UK primary studies examining delayed diagnosis for TB below.

14.10 Overall summary of findings (UK primary studies)

Data on the prevalence of late diagnosis in the UK were limited. One study found that 50% of a small sample of patients prescribed antibiotics prior to confirmation of TB diagnosis experienced treatment delay. Another small study found that, of 62 patients with TB, only 4 out of 38 in-patients had been diagnosed prior to admission.

Being female, older, of white ethnicity or socio-economically deprived was associated with delays in the initiation of treatment.

Among White and UK born patients, shorter intervals were experienced by the most deprived. Recent migrants were less likely to experience delays, as were patients with pulmonary rather than extra-pulmonary disease.

Patient denial, delayed presentation and non-compliance were identified as barriers to diagnosis. Among GPs, a low index of suspicion, a lack of knowledge and sub-optimal clinical-patient communication were identified as barriers to diagnosis.

One small study investigating the utilization of healthcare resources by patients with TB demonstrated a very high rate of in-patient care, judged to be a consequence of the emergency admission of acutely ill, previously undiagnosed cases.

Both screening and case management support components of the London 'Find and Treat' outreach service for hard to reach patients with TB were found to be cost effective.

An educational programme resulted in the improved identification of active and latent tuberculosis, a higher percentage of new registrations screened for TB, and higher median numbers of tuberculin skin tests being carried out in intervention practices compared with controls.

14.11 Included Studies

Five studies, all carried out in London, carried out retrospective case reviews to identify delays in the diagnosis of TB. Craig et al. (2009) tried to determine whether prior antibiotic treatment for presumed bacterial infection led to delays in diagnosing TB. Field et al. (2011) used a TB process-based performance review tool to identify "missed opportunities" for timely and accurate diagnosis among TB patients, 13 of which were from London. Kothari et al. (2005) conducted a study, one of the aims of which was to identify any problems and difficulties in the diagnosis and management of TB associated with pregnancy. Lewis et al. (2003) examined the records of 93 patients to determine the duration of delay between the onset of symptoms in patients with TB and the time it takes for them to be correctly diagnosed and treatment started. White et al. (2002) identified potentially remediable delays in diagnosis and initiation of therapy by examining the records of 83 patients of a NHS trust in East London.

Three studies conducted secondary analyses of national surveillance data (Abubakar et al. 2008, French et al. 2009, Rodger et al. 2003). Abubakar et al. (2008) reported the median time to diagnosis from onset of symptoms in paediatric cases of TB in England and Wales, 1999 to 2006. French et al. (2009) investigated the association between socio-economic deprivation and TB treatment delays in England, 2000 to 2005. Rodger et al. (2003) analysed surveillance data collected by doctors and from an anonymised national survey for cases of TB in London from 1998 to 2000 to investigate factors independently associated with delayed diagnosis.

Two qualitative studies used interviews to examine factors associated with delayed diagnosis of TB. Metcalf et al. (2007) identified a number of barriers to prompt diagnosis in a study investigating the process of diagnosing TB in UK primary care. Nnoaham et al. (2006) conducted a study intended to describe the perceptions and experiences of African patients with TB in London, focusing on issues relating to diagnosis, treatment adherence and stigma.

Griffiths et al. (2007) undertook a cluster randomised controlled trial in order to evaluate an outreach programme promoting screening for TB in people registering in primary care in a UK primary health care district (Hackney, East London).

Finally, Jit et al. (2011) undertook an economic evaluation to assess the cost effectiveness of outreach service for diagnosing and managing hard to reach individuals with active tuberculosis in London.

The characteristics of the studies examining late diagnosis of TB are presented in table 14.5.

Number of contributing studies: 12

Table 14.5: Characteristics of UK primary studies investigating delays in the diagnosis of TB.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Abubakar et al. 2008 [High]	Cross-sectional survey.	England and Wales.	*Sample size*: 3563 All children under the age of 16 years reported with TB to the national enhanced surveillance system between 1999 and 2006 were included. *Gender* Male: 48% *Age* 0-4: 31% 5-9: 24% 10-14: 36% 15: 10% *Ethnicity* White: 16% Black Africans: 28% Pakistani: 20% Indian: 11% Bangladeshi: 4% Black Caribbean: 3% Other/ Unknown: 19%	Tuberculosis Cases included confirmed disease due to *M. tuberculosis* complex infection or disease ''other than culture confirmed'' (a clinician's judgement based on clinical features with or without radiological, histological or tuberculin skin test evidence of TB, and the decision to treat a patient with a full course of more than two anti-TB drugs). Pulmonary cases included patients with TB involving the lungs and/or tracheobronchial tree, with or without a diagnosis of extra-pulmonary TB, while other sites of disease were classified as extrapulmonary TB and the specific organ or system affected reported.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Craig et al. 2009 [Medium]	Retrospective case review.	London.	*Sample size*: 83 Adults with culture-confirmed pulmonary TB at a single metropolitan centre. *Gender* Male: 63% *Age* Median (range): 34(16-34) *Place of birth* UK-born: 35% *Born- abroad time in UK* < 1 year: 25% > 1 year: 39% Not known: 1%	Tuberculosis Culture-confirmed pulmonary TB. Delayed diagnosis Duration of symptoms was defined as that from symptom onset to first presentation to primary care, either emergency department (ED) or GP, and was categorised as < or > 3 months. Symptom onset was defined according to that recorded in the original ED clerking, from GP referral letters or from our case notes. Delay in treatment was defined as >8 weeks from the patient's first presentation to a primary care doctor or ED to start of specific anti-tuberculosis treatment. This period was chosen to account for the possible delay while awaiting a maximal 6 week mycobacterial culture if smear-negative, plus time for the treating clinician to act on the result.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Field et al. 2011 [Medium]	Retrospective case review using a TB Process-Based Performance Review (TB-PBPR) tool, developed to identify "missed opportunities" for timely and accurate diagnosis of TB.	London.	*Sample size*: 13 All patients registered with the TB programme at the Royal Free Hospital (RFH), London, and who died between January 2004 and December 2007 (n=22), of which clinical notes were available for 13 cases, who did not differ r significantly in age, sex or ethnicity from cases without notes. *Gender* Male: 60% *Age* Median (range) 46 (24-69) *Comorbidities* HIV infected: 39%	<u>Delayed diagnosis</u> The TB-PBPR tool identifies 14 clinical actions which, if carried out, should minimize the number of missed diagnoses: eliciting TB symptoms constitutes 1, clinical examination 6 and clinical investigations 7. "Missed opportunities" are identified as errors causing potential failure to make timely and accurate clinical diagnoses.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
French et al. 2009 [High]	Cross-sectional survey.	England.	*Sample size*: 40779 TB cases reported to the Enhanced Tuberculosis Surveillance (ETS) system for England during the period 2000-2005. *Gender* Male: 55% *Age* Median 36 years (IQR 26-54) *Place of birth* Non-UK born: 68% *Ethnicity* White: 26.7% Black Caribbean: 2.3% Black African: 20.1% Indian/ Pakistani/ Bangladeshi: 40.8% Other: 10.1%	<u>Tuberculosis</u> TB cases were culture-confirmed disease due to *M. Tuberculosis* complex or other cases meeting the following criteria a) a clinician's judgement that the patient's clinical or radiological signs were compatible with TB and b) a clinician's decision to treat the patient with a full course of anti-TB treatment. <u>Delayed diagnosis</u> The interval to start of treatment was defined as the total number of days between onset of symptoms (as reported by the patient) and start of treatment, or if this was missing, date of diagnosis. The ETS system does not collect information on the date that patients first present to health-care services, and it was not possible to separate patient delays (i.e. delay from onset of symptoms to presentation to healthcare services), from healthcare delays (i.e. delay from patient presentation to initiation of treatment).

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Griffiths et al. 2007 [High]	Cluster randomised controlled trial.	Hackney, East London.	*Sample size* Intervention practices (n=25): 44986 patients. Control practices (n=25): 48984 patients. *Gender* Intervention group: male 47% Control group: male 46% *Age (Mean years)* Intervention group: 29 Control group: 26 *Ethnicity* White (intervention): 45% White (control): 42% Black (intervention): 22% Black (control): 24% South Asian (intervention): 9% South Asian (control): 10% *Mean no. new immigrants per practice* Intervention group: 248 Control group: 272	Tuberculosis Not specified.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Jit et al. 2011 [Medium]	Economic evaluation using a discrete, multiple age cohort, compartmental model of treated and untreated cases of active tuberculosis.	London.	*Sample size*: 620 Hard to reach individuals with active pulmonary TB screened or managed by the Find and Treat service (48 mobile screening unit cases, 188 cases referred for case management support, and 180 cases referred for loss to follow-up), and 252 passively presenting controls from London's enhanced tuberculosis surveillance system.	<u>Tuberculosis</u> Active pulmonary TB.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Kothari et al. 2005 [Medium]	Retrospective case review.	London.	*Sample size*: 32 pregnant women All women with TB who conceived on antituberculous treatment, or had onset of symptoms or diagnosis made in pregnancy or the immediate postpartum period (6 weeks), and booked for antenatal care at a District General Hospital located in Ealing, Hammersmith and Hounslow Health authority. *Ethnicity* Somalian: 14(44%) Other Black African: 2(6%) Indian: 9(28%) Pakistanki: 3(9%) Afghanistani: 4(13%) *Place of birth* UK-born: 4(12%) *Born-abroad time in UK:* < 5 years: 21(66%) *Unemployed*: 16(50%)	<u>Tuberculosis</u> Pulmonary and extra-pulmonary TB.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Lewis et al. 2003 [Medium]	Retrospective case review.	East London.	*Sample size*: 93 *Gender* Male: 49% *Age* Median (range): 31 (1-81) *Ethnicity* Indian: 63% African:27% Other: 10%	Tuberculosis Not specified. Delayed diagnosis Patient delay: time from the onset of first symptom of TB to time when the patient was first seen by a doctor for that symptom. Healthcare system delay: time between first being seen by a doctor for a symptom of TB and start of treatment. Total delay: the sum of patient delay and healthcare system delay.
Metcalf et al. 2007 [High]	Qualitative study with paired, semi-structured interviews.	South-East Wales.	*Sample size* Patients: 17; GPs: 16 Patients diagnosed with TB in the previous 6 months and GPs involved with their care. *Gender* Patients: Male 11 GPs: Male 12 *Age* Patients: range 19–80 years GPs: range 30–66 years *Ethnicity* Patients: Non-Caucasian 8 GPs: Non-Caucasian 3	Tuberculosis Pulmonary and extra-pulmonary TB.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Nnoaham et al. 2006 [Medium]	Qualitative study with in-depth interviews.	Hackney, East London.	*Sample size* : 16 Consenting adults (≥18 years) attending a clinic for TB treatment at the Homerton University Hospital in Hackney, East London, who were born in Africa, self-identified as African and were willing to be interviewed in English. *Gender* Male: 10 *Age* Median (range):34 (19-46) *Years since entry into UK* < 5 yrs: 7(44%), range 2-25 yrs	<u>Tuberculosis</u> Not specified.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
Rodger et al. 2003 [Medium]	Cross-sectional survey.	London	*Sample size* : 853 Cases of TB in London from 1998 to 2000 identified from surveillance data collected via an anonymised national survey. *Gender* Male: 509(60%) *Age* <40 years: 511(60%) ≥40 years: 337(40%) *Ethnicity* White: 263(31%) Black: 267(31%) Indian Subcontinent: 224(26%) Other: 88(10%) *Place of birth* UK-born: 240(28%) Other: 542(64%) *Years since entry into UK* <2 years: 49(6%) 2-5 years: 180(21%) >5 years: 204(24%)	Tuberculosis Pulmonary TB: positive result in smear tests of pulmonary sputum. Delayed diagnosis Delay in diagnosis was calculated as the number of days between onset of symptoms and diagnosis or the start of treatment (which were on the same day in cases with both recorded). Delay was characterised as greater than the median, or at or less than the median.

Study / Year [Quality Grade]	Research Design	Region	Participant characteristics	Disease state / condition
White et al. 2002 [Medium]	Retrospective case review.	Tower Hamlets, East London.	*Sample size* : 62 Residents of Tower Hamlets treated for drug-sensitive TB in the in-patient and out-patient departments of an NHS trust. *Ethnicity* Bangladeshi: 35 Somalian: 8 Indian: 3 Pakistani: 2 Chinese: 2 Non-Somalian Black African: 2 Indonesian: 1 White (UK): 7 White (non-UK): 1	Tuberculosis Pulmonary and extra-pulmonary TB with diagnosis of drug sensitive TB on the basis of lab sensitivity testing or on an assessment of low risk of resistant disease combined with a favourable outcome to standard clinical therapy.

14.12 Intervals for different aspects of the diagnostic pathway for TB

Table 14.6 presents the median number of days for various intervals within the diagnostic pathway for TB. It is possible that the variation between studies is attributable to the different study populations under examination i.e. children, adults, patients born in Africa, pregnant women.

Table 14.6: Median number of days for various intervals within the diagnostic pathway for TB.

Study	Onset of symptoms to presentation	Onset of symptoms to diagnosis	Presentation to diagnosis	Presentation to treatment	Onset of symptoms to treatment
Abubakar et al. (2008) n=3563		37, IQR: 13-89			
French et al. (2009) n=40779					67, IQR: 30 -131
Kothari et al. (2005) n=32	31	86	32		
Lewis et al. (2003) n=93	63, range: 0-728			35, range: 4-1470	126, range: 4-1533
Nnoaham et al. (2006) n=16		35, range: 14-280			
Rodger et al. (2003) n=853					49, range: 14-103

The interval between presentation and diagnosis, and the interval between presentation and treatment should be similar assuming treatment is initiated immediately upon diagnosis. Kothari et al. (2005) reported a median of 32 days between presentation and diagnosis in pregnant women, whereas Lewis et al. (2003) reported a median number of 35 days between presentation and treatment for 93 residents of East London.

The median interval of 126 days between onset of symptoms to treatment reported by Lewis et al. (2003) was found to be almost double that reported by French et al. (2009), and two and a half times longer than that reported by Rodger et al. (2003). However, French et al. (2009) and Rodger et al. (2003) employed national surveillance data to conduct studies examining much larger populations.

French and colleagues (2009) employed national surveillance data to examine the association between socio-economic deprivation and TB treatment delays in

England. Median intervals between onset of symptoms and treatment, along with hazard ratios for the association between TB case characteristics and the interval to initiation of TB treatment, as reported by French et al. (2009) are presented in Table 14.7.

Table 14.7: French et al. (2009) Median intervals between onset of symptoms and treatment/ hazard ratios for the association between characteristics of TB patients and interval to treatment

Medical/Demographic Characteristic	Number of cases (%)	Median interval days (IQR)	Univariable Hazard Ratio (95% CI) [HR <1 indicates longer interval]	P value
Deprivation quartile 1 (least deprived)	5925(27.1)	70(31-137)	Ref.	< 0.001
Deprivation quartile 2	5226(23.9)	66(29-128)	1.04 (1.00 to 1.08)	
Deprivation quartile 3	5063(23.2)	65(28-124)	1.07(1.03 to 1.11)	
Deprivation quartile 4 (most deprived)	5633(25.8)	71(32-134)	1.00 (0.96 to 1.04)	
Age 0-14 years	1088(4.8)	37(12-89)	1.40 (1.31 to 1.49)	
Age 15-44 years	13463(58.9)	66(30-126)	Ref.	< 0.001
Age 45-64 years	4601(20.1)	77(35-148)	0.87 (0.84 to 0.90)	
Age ≥65	3703(16.2)	71(31-142)	0.92 (0.89 to 0.95)	
Sex Male	12491(54.7)	65(30-123)	Ref.	< 0.001
Sex Female	10340(45.3)	71(31-140)	0.90 (0.87 to 0.92)	
White	6030(26.7)	75(33-145)	0.97 (0.94 to 1.00)	
Black Caribbean	513(2.3)	67(31-137)	0.99 (0.90 to 1.08)	
Black African	4536(20.1)	58(26-109)	1.20 (1.16 to 1.25)	
Indian/Pakistani/Bangladeshi	9219(40.8)	71(32-135)	Ref.	< 0.001
Other ethnicity	2284(10.1)	61(24-121)	1.09 (1.04 to 1.14)	
Born in UK	6954(32.2)	70(31-137)	Ref.	< 0.001
Born abroad, UK entry <2 years ago	3022(14.0)	59(26-111)	1.17 (1.12 to 1.22)	
Born abroad, UK entry ≥ 2 years ago	9543(44.3)	72(34-138)	0.98 (0.95 to 1.01)	
Born abroad, year of entry missing	2047(9.5)	57(21-112)	1.17 (1.11 to 1.23)	

Medical/Demographic Characteristic	Number of cases (%)	Median interval days (IQR)	Univariable Hazard Ratio (95% CI) [HR <1 indicates longer interval]	P value
Extra-pulmonary TB	9370(41.1)	76(34-153)	Ref.	<0.001
Sputum smear positive pulmonary TB	5683(25.0)	61(27-110)	1.35 (1.30 to 1.39)	
Other pulmonary TB	7723(33.9)	64(28-122)	1.24 (1.20 to 1.27)	
No previous TB diagnosis	18739(91.0)	69(31-132)	Ref.	0.047
Previous TB diagnosis	1864(9.0)	71(32-140)	0.95 (0.91 to 1.00)	
Total	22856 (100.0)	67(30-131)	-	-

French and colleagues found that the interval between onset of symptoms and initiation of treatment was longer among the least deprived and most deprived compared to those in the middle two quartiles. Longer intervals were experienced by the most deprived black Africans Indians/Pakistanis/Bangladeshis and recent UK entrants (see Table 14.7). However, among white and UK born patients, *shorter* intervals were experienced by the most deprived (Adjusted HR 1.09, 95% CI 1.01 to 1.17 and Adjusted HR 1.08, 95% CI 1.01 - 1.16, respectively).

Table 14.7 also shows that longer intervals were experienced by older patients, females, those of white ethnicity, those born in the UK, foreign born individuals with UK entry more than two years prior to diagnosis, patients with extra-pulmonary disease and those with a previous TB diagnosis (French et al. 2009).

Examining data for 64 patients, Lewis et al. (2003) found a median patient delay of 9 (range 0-104) weeks and a median healthcare delay of 5(range 0.5-210) weeks and noted that patient delay was significantly longer than healthcare system delay (p = 0.019). Lewis et al. (2003) presented a longer interval for patients with smear positive pulmonary disease than French and colleagues' median of 61 days. Lewis et al. (2003) reported that patient delay alone contributed a median of 60 (range 14 – 511) days and doctor delay 25 (range 0-294) days. However, it must be noted that these findings relate to only 15 patients in comparison with the sample (n=5683) analysed by French et al. (2009).

Abubakar et al. (2008) also used national surveillance data (n=3563) to determine the median time to diagnosis from onset of symptoms in paediatric cases of TB in England and Wales. Median time to diagnosis from onset of symptoms was 15 (IQR 5–50) days in those with miliary disease, 90 (IQR 48–249) days in those with bone tuberculosis, 50 (IQR 31–207) days in those patients who died and 33 (IQR 11–77) in patients completing treatment. Abubakar and colleagues found a median duration between arrival in the UK and diagnosis of TB of two years (IQR 1–4) which varied by ethnicity with a median of 1 year for white, Black African and Black Caribbean children, 2 years for Pakistani children and 3 years for Indian and Bangladeshi children.

Kothari et al. (2006) reported a median delay in diagnosis of 180 days for women with extra-pulmonary TB (n=17) compared to 45 days for those with pulmonary TB (n=12).

Rodger et al. (2003) found a geometric mean delay in days of 72 (95% CI 63 to 80) among white patients and 43 (95% CI 39 to 45) among all other ethnic groups, 72 (95% CI 66 to 77) among women and 61 (95% CI 56 to 65) among men, and 64 (95% CI 55 to 74) among those aged >40 years and 45 (95% CI 40 to 51) among patients aged < 40 years.

14.13 Prevalence

Two primary studies provided data regarding the prevalence of delayed diagnosis of TB (Craig et al. 2009, White et al. 2002).

In their study examining the effect of prior antibiotic treatment for presumed bacterial infection on delays in diagnosing TB, Craig et al. (2009) found that a delay in treatment (defined as >8 weeks from first presentation) occurred in 21 (50%) of 42 patients who received antibiotics, but 0/21 (0%) in the group not prescribed antibiotics. This difference was highly significant (p = 0.001). Symptomatic improvement did not predict delay in diagnosis: 9/21 patients with no delay improved compared to 11/21 patients who were delayed (p = 0.76).

White et al. (2002) found that of 62 residents of Tower Hamlets with TB, only 4 of 38 patients admitted to hospital had been diagnosed prior to admission.

14.14 Determinants

Nine of the included studies investigated determinants of delayed diagnosis of TB (Craig et al. 2009, Field et al. 2011, French et al. 2009, Kothari et al. 2005, Lewis et al. 2003, Metcalf et al. 2007, Nnoaham et al. 2006, Rodger et al. 2003, White et al. 2002).

The determinants of late diagnosis of tuberculosis are presented in table 14.8 below.

Table 14.8: Determinants of late diagnosis of tuberculosis

	Determinant (number of studies) Association with delayed diagnosis: Positive (+) delayed diagnosis more likely; Negative (–) delayed diagnosis less likely; None (□) no association with delayed diagnosis; NS not significant.
Demographic Determinants	**Female Gender (2)** French et al. 2009 (+) [HR 0.90, 95% CI 0.87 to 0.92] Rodger et al. 2003 (+) [Adjusted OR 1.42, 95% CI 1.1 to 1.9, p = 0.01] **Older Age (3)** French et al. 2009 (+) - 0-14 yrs *vs* 15-44 yrs (-) [HR 1.40, 95% CI 1.31 to 1.49, p < 0.001] - 45-64 yrs *vs* 15-44 yrs (+) [HR 0.87, 95% CI 0.84 to 0.90, p < 0.001] - ≥65 yrs *vs* 15-44 yrs (+) [HR 0.92 95% CI 0.89 to 0.95, p < 0.001] Kothari et al. 2006 (□) No differences in age between those who presented late and those who did not. Rodger et al. 2003 (+) - ≥ 40 yrs *vs* < 40 yrs (+ NS) [Adjusted OR 1.18, 95% CI 0.87 to 1.62, p = 0.11] **Place of birth (1)** Rodger et al. 2003 (□) **White Ethnicity (2)** French et al. 2009 (+) - White *vs* Indian/Pakistani/Bangladeshi (+) [HR 0.97, 95% CI 0.94 to 1.00, p < 0.001] - Black Caribbean *vs* Indian/Pakistani/Bangladeshi (+ NS) 0.99, 95% CI 0.90 to 1.08, p < 0.001] - "Other" *vs* Indian/Pakistani/Bangladeshi (-) 1.09, 95% CI 1.04 to 1.14, p < 0.001]

	Determinant (number of studies) Association with delayed diagnosis: Positive (+) delayed diagnosis more likely; Negative (–) delayed diagnosis less likely; None (□) no association with delayed diagnosis; NS not significant.

	Rodger et al. 2003 (+)
	  - Black *vs* White [Adjusted OR 0.52, 95% CI 0.33 to 0.80, p = <0.05]
	  - Indian Subcontinent *vs* White [Adjusted OR 0.64 95% CI 0.42 to 0.99, p = <0.05]
	  - "Other *vs* White [Adjusted OR 0.73 95% CI 0.41 to 1.29, p = <0.05]
	
	Longer residency in UK (3)
	
	French et al. 2009 (+)
	  - Born abroad, UK entry <2 years ago *vs* UK-born (-) [HR 1.17, 95% CI 1.12 to 1.22, p < 0.001]
	  - Born abroad, UK entry ≥ 2 years ago *vs* UK-born (+) [HR 0.98, 95% CI 0.95 to 1.01, P < 0.001]
	
	Kothari et al. 2006 (-) Resident < 16 months *vs* Longer residency [OR 2.14, 95% CI 0.44 to 10.53]
	
	Rodger et al. 2003 (+) Resident > 5 years *vs* Resident < 2 years [OR 2.65, 95% CI 1.34 to 5.25, p = 0.01]
	
	Lower Socio-economic Status (2)
	
	French et al. (2009) (+)
	  - Most deprived Black Africans *vs* Least Deprived [Adjusted HR 0.84, 95% CI 0.77 to 0.92, p < 0.001]
	  - Most deprived Indians/Pakistanis/Bangladeshis *vs* Last Deprived [Adjusted HR 0.93, 95% CI 0.88 to 0.99, p = 0.014]
	  - Most deprived Recent UK Entrants vs Least Deprived [Adjusted HR 0.88, 95% CI 0.79 to 0.97, p = 0.012]
	
	Kothari et al. 2006 (□) No differences in employment status between those who presented late and those who did not.

	Determinant (number of studies) Association with delayed diagnosis: Positive (+) delayed diagnosis more likely; Negative (–) delayed diagnosis less likely; None (□) no association with delayed diagnosis; NS not significant.

Medical Determinants	**Extra-pulmonary Disease (3)**
	
	French et al. 2009 (+)
	   - Sputum Smear Positive Pulmonary *vs* Extra Pulmonary [HR 1.35, 95% CI 1.30 to 1.39, p < 0.001]
	   - Other pulmonary *vs* Extra Pulmonary [HR 1.24, 95% CI 1.20 to 1.27, p < 0.001]
	
	Kothari et al. 2006 (+) OR for extra-pulmonary TB vs pulmonary TB was 1.39 (95% CI 0.26 to 7.3) among women with delayed diagnosis due to non-specific symptoms. Trend towards extra-pulmonary TB in late presenters compared with women who did not present late: OR 1.64, 95% CI 0.32 to 8.45.
	
	Lewis et al. 2003 (+) Pulmonary disease associated with shorter total delay in starting treatment compared with extra-pulmonary disease (p = 0.035).

System Determinants	**Process of Care (3)**
	
	Craig et al. 2006 (+) Prior anti-biotic treatment vs no prior treatment (p = 0.001) Initial antibiotic treatment in patients with TB led to a delay in diagnosis that appeared to arise not from symptomatic improvement, but from prolongation in process of care.
	
	French et al. 2009 (+) Previous diagnosis TB vs No previous diagnosis (HR 0.95, 95% CI 0.91 to 1.00, p = 0.047]
	
	White et al. 2002
	   - Undue delays in performing relevant investigations and/or reviewing results.
	   - Slow onward referral to respiratory team for advice on treatment.

	Determinant (number of studies) Association with delayed diagnosis: Positive (+) delayed diagnosis more likely; Negative (–) delayed diagnosis less likely; None (□) no association with delayed diagnosis; NS not significant.

	Access (1)
	
	Metcalf et al. 2007
	   - Patients did not find it difficult to access their GP and were often seen within a few days.
	   - GPs suggested increasing workload as a possible factor in delaying the diagnosis of TB, as they might simply have been too busy to consider more unusual diagnoses.
	   - Continuity of care suboptimal, with patients being seen by a number of different doctors, from general practice and secondary care, before the diagnosis was made.

Knowledge, beliefs and attitudes of patients	**Fear /Denial (2)**
	Metcalf et al. 2007
	   - Patients reported reluctance in presenting and attending for investigations because they were scared, in fear of wasting medical time, or in denial of possible diagnoses.
	   - Patient health beliefs led to withholding of information, delayed presentation, and lack of compliance with investigations.
	
	Fear/ Denial contd…
	
	Nnoaham et al. 2006
	   - Denial of diagnosis: those who did not accept TB diagnosis often had misconceptions about the nature of their illness and had no prior experience of TB in a known or close person.
	
	Symptom misinterpretation (2)
	
	Metcalf et al. 2007
	   - The majority of patients suspected alternative diseases including cancer, infection, and depression.
	
	Nnoaham et al. 2006
	   - The majority of patients misinterpreted their initial symptoms, attributing them to flu, food poisoning, boils or strenuous activity.

	Determinant (number of studies) Association with delayed diagnosis: Positive (+) delayed diagnosis more likely; Negative (–) delayed diagnosis less likely; None (□) no association with delayed diagnosis; NS not significant.
Knowledge, beliefs and attitudes of clinicians	**Low index of suspicion (1)** Metcalf et al. 2007 - GPs had a relatively low index of suspicion for TB, except in classical presentations, or as the presentation of an unusual case evolved. - TB often diagnosed as a result of casting a wide net of investigations, rather than clinically suspecting TB and ordering a narrow range of relevant tests. - GPs proposed differential diagnoses included (in order of frequency): malignancies; lower respiratory tract infection; asthma; chronic obstructive pulmonary disease; pneumothorax; pulmonary embolus; diabetes; depression; viral illness; malaria; and arthritis. **Lack of Knowledge (1)** Metcalf et al. 2007 - GPs reported lack of recent knowledge about TB, due to insufficient training. - Most GPs were aware of local specialist services but detailed knowledge of these services was lacking. Particular confusion surrounded the current status of the BCG immunisation programme. **Suboptimal clinician–patient communication (1)** Metcalf et al. 2007 - No patient reported being asked by GPs what they thought was causing their symptoms. - Patients' report suggestions that they had TB being rejected by GPs. - Patient had to persuade the GP to investigate for TB. **Other (1)** Metcalf et al. 2007 - GPs over-reliance on knowledge of the social circumstances of patients, e.g. housing conditions, country of origin, drug misuse, might have delayed diagnosis in cases where such factors were not an issue.

Determinants: Key Findings

Demographic

- Gender: two studies provided evidence that being female was associated with delays.

- Age: two studies provided evidence that older age was associated with delays.

- Place of birth: One study found no association between place of birth and delays to diagnosis.

- Ethnicity: two studies found that longer intervals to diagnosis/treatment were experienced by those of white ethnicity.

- Socio-economic status: Longer intervals were experienced by the most deprived individuals from the Indian Subcontinent, Black Africans and recent UK entrants, but among White and UK born patients, *shorter* intervals were experienced by the most deprived.

- Longer residency in the UK: One small study found that shorter residency in the UK was associated with delays to diagnosis. However, two studies employing national surveillance data found that recent migrants were less likely to experience delays.

Medical

- Site of disease: Three studies found that extra-pulmonary disease was associated with delays to diagnosis.

System

- Process of care: previous antibiotic treatment and previous diagnosis of TB were associated with delays to diagnosis and to the initiation of treatment respectively.
- Slow onward referral was associated with treatment delay.

Knowledge, beliefs and attitudes of patients

- Fear: denial, delayed presentation and patient non-compliance were identified as barrier to diagnosis.
- Symptom misinterpretation: the majority of patients attributed their symptoms to a cause other than TB.

Knowledge, beliefs and attitudes of clinicians

- Low index of suspicion: GPs reported that they had a relatively low index of suspicion for TB except in classical presentations.

- Lack of knowledge: GPs reported lack of recent knowledge about TB, due to insufficient training.
- Suboptimal clinician–patient communication: patients reported that their suggestions that they might have TB were rejected by GPs.

14.15 Outcomes

Two studies provided data regarding the outcomes of delayed diagnosis of TB (Kothari et al. 2006, White et al. 2002).

Kothari et al. (2006) did not report any maternal mortality among their sample of 32 pregnant women, 21(65%) of whom experienced delayed diagnosis due to an identifiable and potentially correctable reason. The authors reported that delay in diagnosis or extra pulmonary tuberculosis did not appear to affect the miscarriage rate, pre term delivery or growth restriction, but noted that the sample size was too small for meaningful statistical analysis.

White et al. (2002) investigated the utilization of healthcare resources by patients with TB and demonstrated a very high rate of in-patient care which they judged to be a consequence of the emergency admission of acutely ill, previously undiagnosed cases. Of 62 patients with TB, 38(61%) had an in-patient stay and 26 of these were admitted acutely ill via the Accident and Emergency Department. Of the 26 patients admitted acutely ill, 16 self-presented and 10 were urgently referred by their GP. Only 4 of the total 62 patients were admitted with previously diagnosed disease. Median in-patient stay was 14 (range 1-144) days.

14.16 Costs Implications

One study used an economic evaluation to assess the cost effectiveness of the 'Find and Treat' outreach service for diagnosing and managing hard to reach individuals with active TB (Jit et al. 2011).

Using a discrete, multiple age cohort, compartmental model of treated and untreated cases of active TB, Jit and colleagues estimated that, on average, the 'Find and Treat' outreach service identified 16 and managed 123 active cases of TB annually in hard to reach groups in London. The service had a net cost of £1.4 million per year and, under conservative assumptions, gained 220 QALYs. The incremental cost effectiveness ratio was £6400-£10 000 per QALY gained (about €7300-€11 000 or $10 000-$16 000 in September 2011). The two 'Find and Treat' components were also cost effective, even in unfavourable scenarios (mobile screening unit (for undiagnosed cases), £18 000-£26 000 per QALY gained; case management support team, £4100-£6800 per QALY gained).

14.17 Interventions

One cluster randomised controlled trial assessing the effect of an educational programme provided data regarding an intervention with the potential to reduce delays in the diagnosis of TB (Griffiths et al. 2007).

14.17.1 Educational Outreach Intervention

The intervention developed by Griffiths et al. (2007) consisted of a multifaceted approach of practice-based education sessions, computerised screening reminder prompts, screening equipment and financial incentive to encourage uptake of the screening intervention. Intervention practice received one outreach practice visit (lasting one hour) carried out by a TB specialist nurse and a local academic GP to promote TB screening and raise awareness of TB as a local public health concern and distribute copies of local TB screening guidelines with algorithms. Computer prompts were incorporated into intervention practice computer systems used for registration health check consultations to remind clinicians to ask the screening questions stipulated in guidelines. Intervention practices were provided with Heaf heads and guns and tuberculin for skin testing. Telephone support by a specialist TB nurse for advice and to receive referrals was supplied to intervention practices. Finally, a financial incentive of £7 was paid to participating practices for every tuberculin skin test carried out. Control practices received no contact and continued with usual care.

14.17.2 Outcomes of educational outreach intervention

Griffiths et al. (2007) identified the primary outcome measure as the proportion of all cases of active TB identified in primary care. Secondary outcomes included the proportion of cases of latent TB identified in primary care, the percentage of new registrations screened for TB and numbers of tuberculin skin tests undertaken.

Yield from screening was low but case identification was augmented by improved case finding with intervention practices demonstrating improved identification of active and latent tuberculosis, a higher percentage of new registrations screened for TB and higher median number of tuberculin skin tests being carried out compared with control practices, as described in further detail below.

Proportion of all cases of active TB identified in primary care
The proportion of cases of active TB identified in primary care was higher in intervention practices than control practices (66/141(47%) *vs* 54/157(34% OR 1.61, 95% CI 1.08 to 2.39. Of the 141 patients diagnosed with active tuberculosis in intervention practices, 37 had registered as new patients during the study and were eligible for a registration health check. Of these, 19(51%) attended for a registration health check. Screening at the health checks identified eight cases of active TB in these patients, with a yield of 0.06% (one in 1684). The remaining cases were identified from improved case finding for existing patients in intervention practices. Control practices had negligible screening rates but did identify one patient with active TB.

Percentage of new registrations screened for TB
In intervention practices 57% (13478 of 23573) of people attending a registration health check were screened for TB compared with 0.4% (84 of 23051) in control practices.

Proportion of cases of latent TB identified in primary care
Although none were identified by screening in registration health checks, intervention practices identified a higher proportion of people with latent TB than did control practices (11/58(19%) vs 6/68(9%) OR 3.45, 95% CI 1.51 to 7.87.

Number of tuberculin skin tests undertaken.
Intervention practices did a median of 67 tuberculin skin tests (range 0 – 427) compared with one (range 0 -30) per control group practice (incident rate ratio 20.6, 95% CI 8.5 to 50.0).

14.18 Types of Delay

14.18.1 Patient delay
Kothari et al. (2006) showed that in 21 pregnant women the most frequent reason for delayed diagnosis due to an identifiable and potentially correctable reason was late presentation (52%), followed by non-specific symptoms (38%) and poor patient compliance and follow-up (10%). Treatment was delayed by a month in one patient not keeping appointments. Another patient defaulted appointments and refused bronchoscopy resulting in a delay in diagnosis of over a year, until sputum culture was positive.

Lewis et al. (2003) found a median patient delay of 9 (range 0-104) weeks and a median healthcare delay of 5(range 0.5-210) weeks and noted that patient delay was significantly longer than healthcare system delay (p = 0.019).

Patient fear, denial, non-compliance and symptom misinterpretation were identified as barrier to prompt diagnosis and treatment (Metcalf et al. 2007, Nnoaham et al. 2006).

14.18.2 Doctor delay
Employing the a TB Process-Based Performance Review (TB-PBPR) tool, developed to identify missed opportunities for timely and accurate diagnosis of TB, Field et al. (2011) identified clinical omissions at four hospitals (one situated in the UK) and at every stage of clinical management. Field and colleagues found a mean of 8.8, 9.8, 7.2 and 2.4 missed opportunities per patient at three South African and one London hospital respectively.

General practitioners' low index of suspicion, lack of knowledge, sub-optimal communication with patients and over-reliance on knowledge of their patients' social circumstances were identified as barriers to the prompt diagnosis and treatment of TB (Metcalf et al. 2007).

14.18.3 System delay
White et al. (2002) reviewed 15 cases and found that in 6 there were undue delays in performing relevant investigations and / or reviewing the result, and in 4 more there was slow onward referral to the respiratory team for the advice on treatment. The time to initiation of therapy for 11 patients exceeded 7 days.

Craig et al. (2009) found that although the median time to diagnosis in subjects receiving antibiotics was prolonged, this was not predicted by treatment response.

The authors concluded that patients receiving antibiotics prior to confirmation of a TB diagnosis experience a process-related delay to starting treatment.

Metcalf et al. 2007 identified GP workload and suboptimal continuity of care as barriers to the prompt diagnosis and treatment of TB.

14.19 Discussion

The preponderance of evidence relating to late or delayed diagnosis of TB was confined to that examining the determinants of delay, or investigating time intervals for various parts of the diagnostic pathway. While nine of the 12 UK primary studies were concerned with populations confined to London, the capital represents the area in the UK where the incidence of TB is of most concern: Jit et al. (2011) note that London has seen a resurgence of TB on a scale not seen in any other western European capital in the past two decades and that the incidence of TB in the London borough of Brent is comparable to that of Karonga District in Malawi.

It is unsurprising that there was little disparity between time delays in low/ high endemic countries, or low/ high income countries, since access to healthcare is likely to be restricted in high endemic, low income countries but typically, the incidence and hence the index of suspicion will be low in both low endemic and high income countries.

With respect to the determinants of delayed diagnosis (including initiation of treatment), both the systematic reviews and the UK primary studies suggested that female sex, older age and socioeconomic deprivation were associated with prolonged intervals to diagnosis. However, a UK primary study demonstrated that among White and UK born patients, *shorter* intervals were experienced by the most deprived. In addition, recent migrants were less likely to experience delays as were patients with pulmonary rather than extra-pulmonary disease. These results may be explained by the fact that TB is more likely to be suspected and investigated among those from ethnic minorities, recent entrants to the UK, and in patients with pulmonary disease presenting with classic symptoms. The finding that delay is experienced by socio-economically deprived ethnic minorities, but not those of a White ethnicity may possibly be explained by a reluctance to seek help among particular ethnic communities where a diagnosis of TB attracts stigma.

Indeed, delayed presentation (due to fear, denial or symptom misinterpretation) was identified as a barrier to diagnosis by both qualitative, UK primary studies (Metcalf et al. 2007, Nnoaham et al. 2006). One UK study (Lewis et al. 2003) found that patient delay was significantly longer than healthcare system delay.

Nevertheless, GPs report a lack of recent knowledge about TB due to insufficient training. Prompt diagnosis and treatment of TB may also be hampered by poor clinician-patient communication and a relatively low index of suspicion for TB among GPs, except in classical presentations. This may be remedied by educating primary care health professionals and raising their awareness of TB. Griffiths et al. (2007) appear to have had success in improving the identification of active and latent tuberculosis, screening a higher percentage of new registrations and

performing more tuberculin skin tests among practices receiving an educational outreach programme. Outside primary care, an evaluation of the impact of an in-hospital TB quality care programme on health provider delay and outcome of newly diagnosed cases in a referral hospital in Taiwan found that the programme halved overall mortality and reduced attributable mortality by 62% (Liu et al.2009).

There was no information about the outcomes of late diagnosis of TB in the four included systematic reviews. One small, UK study investigating the utilization of healthcare resources by patients with TB demonstrated a very high rate of in-patient care, judged to be a consequence of the emergency admission of acutely ill, previously undiagnosed cases. A second UK study found that delay in diagnosis or extra pulmonary tuberculosis did not appear to affect the miscarriage rate, pre term delivery or growth restriction, but the authors noted that their sample size was too small for meaningful statistical analysis. In contrast, Jana et al. (1994) examined the perinatal outcome of 79 pregnant women with pulmonary tuberculosis compared with that of 316 normal pregnant women of similar age, parity and socioeconomic status and found that maternal tuberculosis carried a highly significant increased risk in terms of birthweight, small for gestational age neonates, prematurity and perinatal death. Jana and colleagues reported that adverse perinatal outcome was pronounced in cases with late diagnosis, incomplete and irregular treatment, and advanced pulmonary lesions.

None of the included systematic reviews provided information on the cost implications of delayed diagnosis of TB. One UK primary study, an economic evaluation, demonstrated that both screening and case management support components of the London 'Find and Treat' outreach service for hard to reach patients with TB were cost effective.

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15. Discussion

15.1 Where is late diagnosis of most concern?

There are four conditions were late diagnosis is of most concern: COPD, Dementia, HIV and Type 1 Diabetes.

COPD has a particularly high prevalence of late diagnosis, with an estimated 80% of cases remaining undiagnosed. Many of these cases are likely to be patients in the milder stages of the disease. Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009). Under-diagnosis was associated with costly hospital admissions for exacerbations of the condition.

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases, with doctors acknowledging their difficulties in distinguishing between dementia and 'normal ageing'. There was some ambivalence about diagnosing patients early because both doctors and families of patients could not see therapeutic value in doing so.

There was evidence to suggest that a substantial proportion (16–51%) of children experience delayed diagnosis in type I diabetes (>24 hours for any reason).

Those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis, which has worrying implications with regard to onward transmission. Data from the Health Protection Agency indicates that 50% of new diagnoses are late in the UK.

There were some conditions where the lateness of the diagnosis had a considerable impact, such as chronic kidney disease and psychosis, leading to high morbidity and mortality, and less likelihood of remission or positive response to treatment. In these two cases, interventions such as early intervention services (psychosis) and decision support software for primary care staff (CKD) have improved the situation.

For myocardial infarction (STEMI) and stroke, the treatment available has improved considerably over the last decade and the health system has been re-organised to deliver the best care. However, patient delay remains an intractable problem and the mass media public awareness campaigns have not been as successful as hoped.

15.2 Who is most likely to experience late diagnosis?

Broadly, late diagnosis affects vulnerable groups such as older people or those living in poverty.

Age was identified as a barrier to early diagnosis in the included research. Older age was distinguished as a determinant of delay in the diagnosis of depression, tuberculosis and COPD. In contrast, younger age was found to be a barrier to diagnosis in those suffering from type 1 diabetes. Delayed diagnosis for older

people might be a consequence of the increased presence of confounding co-morbidities in this age group. Alternatively, delayed diagnosis for older patients may be a result of beliefs held by doctors and patients that nothing can be done to halt progression (as was the case for dementia patients), that deterioration in health is to be expected as age increases, or simply of ageism.

Females were more likely to experience a delayed diagnosis of dementia, type I diabetes or tuberculosis.

A lower socio-economic status was implicated in delayed diagnosis both for type I diabetes and tuberculosis. Delayed diagnosis among less affluent populations may occur due to access difficulties or that fact that generally, less prosperous people demonstrate poorer health and are more likely to suffer from the co-morbidities which contribute to missed diagnoses. Low education levels were associated with delay in dementia, tuberculosis and type I diabetes.

Belonging to an ethnicity minority was associated with presenting with diabetic ketoacidosis at diagnosis of type I diabetes in children and young adults. White patients were more likely to experience delays in the treatment of tuberculosis than ethnic minorities. Language barriers were mentioned by doctors when discussing communication problems with patients suffering from dementia.

15.3 Categorising delay

We found very little research examining administrative, organisational or procedural (system) determinants of diagnostic delay. System barriers to diagnosis require further investigation. Among this type of determinant, resource constraints and access issues were more frequently discussed than organisational/management issues. This may simply be a reflection of the fact that these factors are easier to record and investigate.

The Hansen model (Hansen et al. 2008) served as a useful starting point for categorising delay in order to create our systematic map. However, types of delay occurring for one condition may be specific to that condition, e.g. where symptoms are slow to appear. Any one model is bound to have limitations when trying to describe delays for the late diagnosis literature across all conditions. Ultimately, universal indicators for delays to diagnosis may be an unattainable goal due the disease-specific nature of delays within a particular condition.

It may be more useful to conceive of delays to diagnosis in terms of the length of intervals within the diagnostic process and factors impacting upon, or prolonging these intervals. However, with the exception of reviews which focused upon delays occurring in the diagnosis of tuberculosis (Sreeramareddy et al.2009, Storla et al. 2005) and myocardial infarction (Boersma et al 2006, De Luca 2008), the included reviews did not present any information with regard to specific time intervals within the diagnostic process. It may be that this practice is not sufficiently established to be described in systematic reviews as yet.

15.3.1 Patient delay

Patient delay was identified as barriers to prompt diagnosis and treatment for a number of conditions including chronic kidney disease, dementia, HIV, stroke, myocardial infarction, epilepsy and tuberculosis. Symptom misinterpretation and lack of knowledge were implicated in delayed presentation. In the case of epilepsy, the patient may be unaware of their condition until an attack is witnessed by another. Fear often appeared to influence patients' help-seeking behaviour.

Three of the four reviews concerning stroke concentrated on studies that described patient delay and its relationship with knowledge of the symptoms and warning signs of stroke. Lack of knowledge of the warning signs of a stroke or a TIA, as well as lack of action needed when a stroke is suspected, were found to be major determinants of delay. There was a similar finding for patients with STEMI.

Patient fear, denial, non-compliance with investigations and symptom misinterpretation were identified as barrier to prompt diagnosis and treatment of tuberculosis. Similarly, patients appeared to delay going to the doctor for fear of the stigma of mental illness associated with a diagnosis of dementia, and the subsequent loss of independence. Patients and their families may not recognise early symptoms of dementia, or may have got used to compensating for their relatives' cognitive deterioration. There was a perception that there were few treatment options for dementia, so early diagnosis was not desirable. Low risk perception, fear of a positive diagnosis and fear of disclosure were all identified as barriers to HIV testing. Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid testing as a result of fear of a positive diagnosis. Fear of disclosure was a particular concern among African communities in the UK. Uptake of testing was inhibited among migrants who feared that HIV status might have a bearing on the immigration process.

It may be difficult to address patient delay, particularly where delays to help-seeking behaviour are influenced by fear (of disease or stigma). Where delay is caused by lack of knowledge, mass media campaigns can be employed to reduce symptom misinterpretation or delay in seeking appropriate help. However, such campaigns can be extremely costly and this review has not identified robust evidence of success. For stroke, public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services. For psychosis, the results of studies reporting on the impact of multi-focus awareness campaigns on reducing treatment delay were mixed and conflicting. With regard to myocardial infarction, the increased use of emergency services from public awareness campaigns has to be of concern as it places extra burdens on the health service and does not appear to result in significant gains to early diagnosis.

15.3.2 Doctor delay

Inadequate knowledge and training were identified as barriers to prompt diagnosis and treatment for chronic kidney disease, COPD, dementia and tuberculosis.

Diagnosing dementia in its early stages was judged to be difficult as symptoms were fluctuating and non-specific. Primary care providers wished to have more education about what constitutes 'normal ageing' so they were able to make accurate diagnoses. They expressed discomfort at using diagnostic tests and wanted greater support and input from specialist colleagues in secondary care. Lack of training in the use of spirometry contributed to the lack of confidence in using the equipment for the diagnosis of COPD. Spirometry was performed more often by those who were confident of interpreting the results. General practitioners' low index of suspicion, lack of knowledge and sub-optimal communication with patients were identified as barriers to the prompt diagnosis and treatment of tuberculosis. The improvement in identification of patients with tuberculosis, produced by a campaign to educate primary healthcare practitioners, suggests that it is possible to remedy deficits in clinical knowledge, although it may be difficult to replicate this success for other diseases or conditions in which a low index of suspicion is not a critical factor.

Communication difficulties were identified as barriers to diagnosis for chronic kidney disease, dementia, HIV and tuberculosis. Difficulties in disclosing and explaining a diagnosis of dementia were reported. Anxiety and reticence were also described among GPs reluctant to discuss HIV testing with patients (even in high-risk groups), which resulted in delays due to onward referral. Patients suggested that GPs failed to adequately communicate the value of HIV testing. Finally, therapeutic nihilism was also exhibited by doctors, who were reluctant to initiate investigations as they were uncertain about what support might be available to dementia patients or what they might offer in support by way of treatment or services. In appears therefore, that factors over and above constraints to consultation time are impacting upon optimal communication between patients and clinicians.

15.3.3 System delay

The most frequently identified system determinants of delays to diagnosis were restricted access, insufficient consultation time and resources constraints. Access issues, in terms of geographical location or knowledge of availability of services, were described for chronic kidney disease, HIV and tuberculosis. GP workload and suboptimal continuity of care were identified as barriers to the prompt diagnosis and treatment of TB. Insufficient consultation time was also described as impeding diagnosis of dementia: the time of a typical visit to a doctor's surgery did not allow for the completion of diagnostic tests. Resource constraints also hindered the early detection of dementia. Doctors also felt discouraged by the low reimbursement for dementia care. There was evidence to suggest that the supply of primary care affects diagnostic rates for COPD. Key informants in the field of HIV and working with African communities in the UK noted that financial and human resources were often lacking in order to target African communities in the UK. Economic evaluations elucidating the cost-effectiveness of earlier diagnosis and treatment, should serve to identify where to direct resources in order to make best use of limited budgets.

15.4 Interventions

Early diagnosis of some conditions may be difficult to improve upon due to non-specific presentation (e.g. dementia) or due to aggressive onset of disease (e.g. type 1 diabetes). Nonetheless, having established whether or not those with a particular condition are likely to experience delayed diagnosis, and the effect that delayed diagnosis will have upon mortality and morbidity, the question immediately arises as to what can be done to promote early diagnosis and prompt treatment. Treatment delay may be considered equivalent to late intervention. However, an unmanageable quantity of literature was generated using terms to capture the concept of "early/late intervention" during the early stages of this review. Thus, literature was sought and examined only where "early/late intervention" and "treatment delay" occured alongside diagnosis terminology. Indeed, much of the literature examining early intervention is focused on the timing of treatment in relation to prognostic or clinical factors rather than undue or avoidable delay. Nevertheless, we must acknowledge that we may have failed to locate a proportion of the literature examining early intervention. Future research may help to identify this potential source of evidence.

For dementia, there was some evidence that doctor education improved the detection of the condition. However, the trials reviewed were not large and so could not present robust findings, and only one was conducted in the UK. An UK educational programme intended for primary care health professionals, resulted in improved identification of active and latent tuberculosis and a higher percentage of new registrations screened for TB in those practices exposed to the intervention.

Multi-component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy for those suffering a stroke. However, public education campaigns were successful in increasing the knowledge of stroke symptoms, but not in improving the awareness of the need to access the emergency services. While the bulk of the literature focused upon delays within primary healthcare, we found relatively few studies examining mass media/patient education campaigns. This may be due to the expensive nature of such campaigns, or concerns about their efficacy or the longevity of their impact.

Specialised early intervention teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, the results with regard to interventions to reduce the duration of untreated psychosis were mixed and conflicting.

There was evidence to suggest that reminder systems produced shorter delays in tuberculosis diagnosis, but more substantive trials are required. Similarly, case finding strategies, targeted at high-risk groups may prove useful for identifying individuals with COPD and tuberculosis.

Medical advances in cardiology have been utilized by the health system to improve emergency care for patients suffering a heart attack. In the last decade, the re-organisation of services so that a majority of patients have rapid access to catheter

laboratories and primary angioplasty, has resulted in lower mortality and morbidity for those patients who present in less than 6 hours from the onset of symptoms.

15.5 Costs

There was very little material about the cost implications of delayed diagnosis, but this may reflect a general dearth of economic data in the biomedical literature as a whole, and in systematic reviews in particular. Although authors of primary studies often report costs or cost-effectiveness, it is rarely the case that they provide data in a format which can be used within systematic reviews. Therefore, the presence of reliable cost-effectiveness data within reviews of reviews, including this one, is scant. Both Brown and Grimes (1995) and Dierick van Daele et al. (2008) have discussed the challenges in obtaining cost-effectiveness data for systematic review.

Economic evaluations need to weigh the initial increase in demand upon services that results from earlier diagnosis against savings attributable to avoiding the treatment of advanced disease, and the avoidance of losses due to individuals remaining socially and economically active. Where diseases are communicable, savings accrued from reduced transmission may be substantial – as has been suggested for HIV.

15.6 Strengths and Limitations

The strength of this rapid systematic review lies in the fact that it has been conducted in accordance with key systematic review principles to ensure that it is transparent, replicable and updateable. The explicit reporting of methods and storage of extracted data online also ensures that it can be subjected to critical appraisal.

Given that the literature examining late diagnosis was extensive, it was necessary to limit the scope of the review. This review focused upon eleven specific conditions – it does not examine the late diagnosis literature in its entirety. Conducting a review of reviews enabled us to cover a broader scope than would otherwise have been possible within the limited time frame available to conform to policy requirements. However, this approach does not allow us to capture nascent concepts within the literature, or those topics that may not be amenable to review methodology.

Indeed, late diagnosis of chronic obstructive pulmonary disease had not yet been subject to systematic review and thus we were required to undertake our own synthesis of primary studies. Likewise, reporting of average time intervals for particular parts of the diagnostic process may not yet have been sufficiently widely adopted in primary studies to the extent that it will be available within systematic reviews.

A significant period of time may elapse between primary research being conducted and its incorporation into a systematic review. This problem is further compounded when conducting a review of reviews. As such, it may be the case that evidence no longer accurately reflects the current picture (e.g. UK renal registry data suggests that late presentation of chronic kidney disease patients has fallen), or that

programmes (e.g. Early Intervention Services for psychosis) are put in place before review-level evidence becomes available.

All included systematic reviews were critically appraised independently by two reviewers with a final judgement being agreed through mutual discussion. Typically, reviews failing to meet a minimum quality threshold would be excluded to instil confidence that the findings of the review were based on sound evidence. However, we were required to sacrifice a minimum quality threshold in order to maximise the data available for syntheses and to promote coverage of the widest possible range of conditions. Nevertheless, the quality scores for each review are presented, and the majority of evidence was of a very good standard (only seven of the 43 reviews included in syntheses scored less than six out of eleven on the AMSTAR critical appraisal checklist). Where we have conducted our own reviews of primary research relating to late diagnosis in COPD, epilepsy and tuberculosis, we have made an assessment of the risk of bias in the primary research. When employing review-level evidence, as far as possible, we have used the results of syntheses and meta-analyses. However, in order to answer questions regarding the prevalence, determinants, outcomes, costs of late diagnosis and interventions to reduce delayed diagnosis, on occasion it was necessary to present the results of individual primary studies within included reviews. We have highlighted any methodological flaws within primary studies where these have been reported, but it should be noted that we have not conducted our own assessment of the risk of bias in individual primary studies included within systematic reviews.

The included systematic reviews contained evidence from a plethora of countries, not all of which have health systems or populations which allow a direct comparison with the state of affairs in the UK. This was particularly the case for the synthesis pertaining to tuberculosis, where a considerable amount of the data related to populations from low and middle income countries with limited generalizability to the UK. In order to obviate this problem, we conducted an additional synthesis of UK primary studies relating to delayed diagnosis of TB.

A major strength of systematic reviews lies in their ability to summarize research in a particular area. However, in the act of summarizing data, detail is lost. As Jepson et al. (2010) note, the evidence provided in reviews is 'twice removed' from the original primary data and has limitations for providing detailed evidence of effectiveness for a particular intervention in a particular population group. Integrating data from multiple reviews may provide a comprehensive, 'wide lens' picture of the research evidence, but difficulties can develop with regard to the applicability of the findings to everyday practice and/or policy decisions due to lack of detail and contextual information. For example, the challenge of incorporating complex interventions into systematic reviews, where information to support applicability (such as intervention content, fidelity, intensity and sustainability) is lacking, has been previously highlighted (Shepperd et al. 2009).Future research may profit from a more focussed look at individual conditions, taking into consideration essential contextual factors such as organisational setting.

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Appendix 1: Search Strategies

BRITISH NURSING INDEX (BNI)
Searched 01.11.11

No.	Database	Search term	Hits
1	BNI	DIAGNOSIS/ OR ANTENATAL DIAGNOSIS/ OR PATIENT ASSESSMENT/ OR SCREENING/	<u>8522</u>
2	BNI	(detect OR detection OR detecting OR "help seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present).ti	<u>1816</u>
3	BNI	(diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic).ti,ab	<u>7671</u>
4	BNI	(late OR later OR early OR earlier OR error OR errors OR wrong OR wrongly OR correct OR correctly OR incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR rapid).ti	<u>5985</u>
5	BNI	(delay OR delays OR delaying OR delayed).ti,ab	<u>700</u>
6	BNI	1 OR 2 OR 3	<u>16694</u>
7	BNI	4 OR 5	<u>6623</u>
8	BNI	6 AND 7	<u>753</u>
9	BNI	exp CANCER/	<u>8718</u>
10	BNI	8 NOT 9	<u>630</u>

CINAHL (Cumulative Index for Nursing and Allied Health)
Searched 28.10.11

S41 S40 AND S23 Search modes - Boolean/Phrase   View Results (3548)
    S40 S24 or S26 or S27 or S28 or S29 or S30 or S31 or S34 or S35 or S39
Search modes - Boolean/Phrase   View Results (386402) View Details Edit
S39 TI ((UK OR U.K. OR "united kingdom" OR Scotland OR Ireland OR
Scottish OR Irish OR Welsh OR Britain OR British OR NHS OR "national
health service" OR PCT OR PCTs OR "Primary Care Trust" OR "Primary Care
Trusts") OR (borough w1 council*) OR (local w1 council*) OR (county w1
council*) OR (local w1 authorit*) OR (district w1 council*)) Search modes
- Boolean/Phrase   View Results (28974) View Details Edit Interface -
S38 S37 AND S23 Search modes - Boolean/Phrase   View Results (3531)
View Details Edit Interface - EBSCOhost
Search Screen - Advanced Search
Database - CINAHL Plus
S37 S24 or S26 or S27 or S28 or S29 or S30 or S31 or S34 or S35 Search
modes - Boolean/Phrase   View Results (379227) View Details Edit
    S35 TI English OR AB English Search modes - Boolean/Phrase   Rerun

S34 S33 NOT S32 Search modes - Boolean/Phrase   Rerun View Details

S33 TX (Manchester OR Birmingham OR Oxford OR Leeds OR Sheffield OR Bradford OR Liverpool OR Newcastle OR Cambridge OR Bristol OR Cardiff OR Belfast OR Edinburgh OR Newcastle OR Glasgow) OR AF (Manchester OR Birmingham OR Oxford OR Leeds OR Sheffield OR Bradford OR Liverpool OR Newcastle OR Cambridge OR Bristol OR Cardiff OR Belfast OR Edinburgh OR Newcastle OR Glasgow) Search modes - Boolean/Phrase   Rerun View

S32 AF (Manchester OR Birmingham OR Oxford OR Leeds OR Sheffield OR Bradford OR Liverpool OR Newcastle OR Cambridge OR Bristol OR Cardiff OR Belfast OR Edinburgh OR Newcastle OR Glasgow) AND AF (USA OR Canada OR Australia) Search modes - Boolean/Phrase   Rerun View Details Edit

S31 (AF London) NOT (AF (new London) OR (London w1 on) OR (London w2 Ontario)) Search modes - Boolean/Phrase   Rerun View Details Edit
 Interface - EBSCOhost
Search Screen - Advanced Search
Database - CINAHL Plus

S30 AF (("UK" OR U.K. OR "united kingdom" OR Scotland OR Ireland OR Scottish OR Irish OR Welsh OR Britain OR British OR NHS OR "national health service" OR PCT OR PCTs OR "Primary Care Trust" OR "Primary Care Trusts") OR (borough w1 council*) OR (local w1 council*) OR (county w1 council*) OR (local w1 authorit*) OR (district w1 council*)) Search modes - Boolean/Phrase   View Results (146331) View Details Edit Interface -

S29 (TX London) NOT (TX (new London) OR (London w1 on) OR (London w2 Ontario)) Limiters - Published Date from: 20010101-20121231; English Language
 Search modes - Boolean/Phrase   Rerun View Details Edit Interface -

S28 SO (British OR English OR Scottish OR Welsh OR Irish) OR AB((UK OR U.K. OR "united kingdom" OR Scotland OR Ireland OR Scottish OR Irish OR Welsh OR Britain OR British OR NHS OR "national health service" OR PCT OR PCTs OR "Primary Care Trust" OR "Primary Care Trusts") OR (borough w1 council*) OR (local w1 council*) OR (county w1 council*) OR (local w1 authorit*) OR (district w1 council*)) Limiters - Published Date from: 20010101-20121231; English Language
Search modes - Boolean/Phrase   View Results (92897) View Details Edit

S27 TX (Wales NOT ("new south wales" OR nsw)) OR AF (Wales NOT ("new south wales" OR nsw)) Limiters - Published Date from: 20010101-20121231;
English Language
Search modes - Boolean/Phrase   Rerun View Details Edit Interface -

S26 TX (England NOT "new England") OR AF (England NOT "New England") Limiters - Published Date from: 20010101-20121231; English Language
Search modes - Boolean/Phrase   Rerun View Details Edit Interface -

S25 S23 AND S24 Limiters - Published Date from: 20010101-20121231; English Language
Search modes - Boolean/Phrase   View Results (1131) View Details Edit Interface - EBSCOhost
Search Screen - Advanced Search
Database - CINAHL Plus

S24 MH "united kingdom+" Limiters - Published Date from: 20010101-20121231; English Language

Search modes - Boolean/Phrase   Rerun View Details Edit Interface -
 S23 S18 NOT S22 Limiters - Published Date from: 20010101-20121231;
English Language
Search modes - Boolean/Phrase   View Results (21531) View Details Edit
S22 S19 OR S20 OR S21 Search modes - Boolean/Phrase   Rerun View
S21 MH "Nucleic Acid Amplification Techniques+" Search modes -
Boolean/Phrase   Rerun View Details Edit Interface - EBSCOhost
S20 MH "Sensitivity and Specificity" Search modes - Boolean/Phrase
Rerun View Details Edit Interface - EBSCOhost
S19 TX rtpcr OR rtqpcr OR rt-pcr OR rt-qpcr OR "rt pcr" OR "rt qPCR" OR
"real time PCR" OR "real-time PCR" OR "real-time qPCR" OR "real time qPCR"
OR "real time polymerase chain reaction" OR "real-time polymerase chain
reaction" OR "delayed development" OR "developmental delay" OR
"likelihood
ratio" OR "likelihood ratios" OR "predictive value" OR "predictive values"
OR specificity OR sensitivity Search modes - Boolean/Phrase   Rerun View
Details Edit Interface - EBSCOhost
S18 S16 NOT S17 Search modes - Boolean/Phrase   View Results (30503)
        S17 MH "Animals+" NOT ((MH "Animals+") AND (MH "Humans+"))
Search
 modes - Boolean/Phrase   Rerun View Details Edit Interface - EBSCOhost
S16 S12 NOT S15 Search modes - Boolean/Phrase   View Results (30662)
View Details Edit Interface - EBSCOhost
S15 S13 OR S14 Search modes - Boolean/Phrase   Rerun View Details
S14 TX neoplas* OR cancer* OR tumor* OR tumour* OR sarcom* OR
carcinoma* OR maligna* Search modes - Boolean/Phrase   Rerun View
 S13 MH "Neoplasms+" Search modes - Boolean/Phrase   Rerun View
S12 S10 OR S11 Search modes - Boolean/Phrase   View Results (38482)
S11 S6 AND S8 Search modes - Boolean/Phrase   Rerun View Details Edit
 S10 S2 OR S9 Search modes - Boolean/Phrase   View Results (21142)
S9 TX misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR
misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR
under-diagnosed OR under-diagnosis OR underdiagnose OR under-diagnose
OR
misdiagnose OR mis-diagnose Search modes - Boolean/Phrase   Rerun View
        S8 S4 OR S7 Search modes - Boolean/Phrase   Rerun View Details
Edit
Interface - EBSCOhost
S7 TI (delay OR delays OR delaying OR delayed) OR AB (delay OR
 delays OR delaying OR delayed) OR TI (late OR later OR early OR earlier
OR error OR errors OR wrong OR wrongly OR correct OR correctly OR
incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR
mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR
rapid
) Search modes - Boolean/Phrase   Rerun View Details Edit Interface -
S6 S1 or S3 or S5 Search modes - Boolean/Phrase   Rerun View Details
S5 MH ("Diagnosis" OR "Diagnosis, Differential" OR "Nursing Diagnosis"
OR "Self Diagnosis" OR "Prenatal Diagnosis") Search modes -
Boolean/Phrase   Rerun View Details Edit Interface - EBSCOhost
S4 MH ("Time Factors" OR "Turnaround Time") Search modes -
Boolean/Phrase   Rerun View Details Edit Interface - EBSCOhost
 S3 MH "Health Screening" Search modes - Boolean/Phrase   Rerun View
Details Edit Interface - EBSCOhost
S2 MH ("Diagnosis, Delayed" OR "Diagnostic Errors" OR "Failure to

Diagnose" OR "False Negative Results" OR "False Positive Results" OR "Early Diagnosis" OR "Early Intervention") Search modes - Boolean/Phrase View Results (16802) View Details Edit Interface - EBSCOhost
 S1 TI (detect OR detection OR detecting OR "help seeking" OR "help-seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present) OR TI (diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic) OR AB (diagnostic OR diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses) Search modes - Boolean/Phrase

CINAHL (Cumulative Index for Nursing and Allied Health)
Searched 02.11.11

No.	Database	Search term	Hits
1	CINAHL	(systematic AND review).ti,ab	15350
2	CINAHL	(detect OR detection OR detecting OR "help seeking" OR "help-seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present).ti	21212
3	CINAHL	(diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic).ti,ab	120108
4	CINAHL	DIAGNOSIS/	2350
5	CINAHL	HEALTH SCREENING/	14578
6	CINAHL	DIAGNOSIS, DIFFERENTIAL/	22265
7	CINAHL	DIAGNOSTIC ERRORS/ OR FAILURE TO DIAGNOSE/ OR EARLY DIAGNOSIS/ OR EARLY INTERVENTION/ OR DIAGNOSIS, DELAYED/ OR FALSE NEGATIVE RESULTS/ OR FALSE POSITIVE RESULTS/	12986
8	CINAHL	NURSING DIAGNOSIS/ OR SELF DIAGNOSIS/ OR PRENATAL DIAGNOSIS/	6563
9	CINAHL	(misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR under-diagnosed OR under-diagnosis OR underdiagnose OR under-diagnose OR misdiagnose OR mis-diagnose).ti,ab	4041
10	CINAHL	TIME FACTORS/ OR TURNAROUND TIME/	52274
11	CINAHL	(late OR later OR early OR earlier OR error OR errors OR wrong OR wrongly OR correct OR correctly OR incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR rapid).ti	68331
12	CINAHL	(delay OR delays OR delaying OR delayed).ti,ab	21367
13	CINAHL	exp NEOPLASMS/	142885
14	CINAHL	(neoplas* OR cancer* OR tumor* OR tumour* OR sarcom* OR carcinoma* OR maligna*).ti,ab	121681
15	CINAHL	2 OR 3 OR 4 OR 5 OR 6 OR 8	168464

No.	Database	Search term	Hits
16	CINAHL	10 OR 11 OR 12	131072
17	CINAHL	15 AND 16	15569
18	CINAHL	7 OR 9	16388
19	CINAHL	17 OR 18	30139
20	CINAHL	19 NOT 13	25033
21	CINAHL	19 NOT 13 [Limit to: Publication Year 2001-2011 and (Language English)]	20148
22	CINAHL	1 AND 21 [Limit to: Publication Year 2001-2011 and (Language English)]	217

COCHRANE LIBRARY (58)/ CENTRAL (4671)/ DARE (126)/ HTA (73)/ NHS EED (160)
Searched 26.10.11

ID	Search	Hits
#1	MeSH descriptor **Diagnosis**, this term only	66
#2	MeSH descriptor **Diagnosis, Differential**, this term only	1278
#3	MeSH descriptor **Incidental Findings**, this term only	17
#4	(detect OR detection OR detecting OR "help seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present):ti	5390
#5	(diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic):ti,ab,kw	67961
#6	MeSH descriptor **Time Factors**, this term only	43089
#7	(late OR later OR early OR earlier OR error OR errors OR wrong OR wrongly OR correct OR correctly OR incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR rapid):ti	25292
#8	(delay OR delays OR delaying OR delayed):ti,ab,kw	18213
#9	(#1 OR #2 OR #3 OR #4 OR #5)	71287
#10	(#6 OR #7 OR #8)	78744
#11	(#9 AND #10)	9935
#12	MeSH descriptor **Delayed Diagnosis**, this term only	4
#13	MeSH descriptor **Diagnostic Errors**, this term only	211
#14	MeSH descriptor **Early Diagnosis**, this term only	259
#15	(misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR under-diagnosed OR underdiagnosis OR under-diagnosis OR underdiagnose or under-diagnose OR misdiagnose or mis-diagnose):ti,ab,kw	311

#16	(#12 OR #13 OR #14 OR #15)	766
#17	(#11 OR #16)	10455
#18	(#17), from 2001 to 2012	6097
#19	MeSH descriptor **Neoplasms** explode all trees	42019
#20	(cancer or cancerous or tumour or tumours or tumor or tumors or sarcoma or sarcomas or carcinoma or carcinomas or neoplastic or neoplasm or neoplasms):ti,ab,kw	66865
#21	(#19 OR #20)	71839
#22	(#18 AND NOT #21)	

HMIC (Health Management Information Consortium)
Searched 26.10.11

1   screening/ or mass screening/ or neonatal screening/ or diagnosis/ or diagnostic services/ or early diagnosis/ or screening policy/ or screening programmes/ or screening services/ (5370)

2   diagnosis/ or clinical diagnosis/ or differential diagnosis/ or early diagnosis/ or prenatal diagnosis/ (2085)

3   diagnosis related groups/ (374)

4   (detect or detection or detecting or "help seeking" or help-seeking or referred or referral or referrals or presentation or presenting or present).m_titl. (2381)

5   (detect or detection or detecting or "help seeking" or help-seeking or referred or referral or referrals or presentation or presenting or present).mp. [mp=title, other title, abstract, heading words] (20311)

6   (delay or delays or delaying or delayed).mp. [mp=title, other title, abstract, heading words] (2336)

7   (late or later or early or earlier or error or errors or wrong or wrongly or correct or correctly or incorrect or incorrectly or missed or missing or miss or mistake or mistakes or mistaken or mistakenly or time or timely or untimely or rapid).m_titl. (6246)

8   exp Early diagnosis/ (120)

9   (misdiagnosis or misdiagnoses or mis-diagnosis or mis-diagnoses or misdiagnosed or mis-diagnosed or undiagnosed or underdiagnosed or under-diagnosed or under-diagnosis).mp. [mp=title, other title, abstract, heading words] (290)

10   1 or 2 or 3 or 4 or 5 (24993)

11   6 or 7 (8440)

12   10 and 11 (1221)

13   8 or 9 (406)

14   12 or 13 (1552)

15   limit 14 to yr="2001 -Current" (925)

16   exp cancer/ (8993)

17   (cancer$ or sarcoma$ or carcinoma$ or maligna$ or tumour$ or tumor$ or neoplas$).mp. [mp=title, other title, abstract, heading words] (12591)

18   16 or 17 (12712)

19   15 not 18 (721)

20   ("developmental delay" or sensitivity or specificity or "predictive value" or "predictive values" or rtpcr or rtqpcr or rt-pcr or rt-qpcr or "rt pcr" or "rt qPCR" or "real time PCR" or "real-time PCR" or "real-time qPCR" or "real time qPCR" or "real time polymerase chain reaction" or "real-time polymerase chain reaction").mp. [mp=title, other title, abstract, heading words] (1946)

21   ("delayed development" or "likelihood ratio" or "likelihood ratios").mp. [mp=title, other title, abstract, heading words] (63)

22   20 or 21 (1979)

23   19 not 22 (673)

PSYCHINFO
Searched 26.10.11/ 02.11.11

S20   S14 and S19   Search modes - Boolean/Phrase
  View Results (6502)
  S19   S15 or S16 or S17 or S18   Search modes - Boolean/Phrase
  View Results (1917593)
  S18   TI English OR AB English   Search modes - Boolean/Phrase
  View Results (101847)
  S17   TX Hammersmith OR Hampshire OR Haringey OR Harlow OR Hartlepool OR Harwell OR Helens OR Hereford OR Hertfordshire OR Highland OR Hounslow OR Hull OR Humber OR Inverclyde OR Inverness OR "Isle of Man" OR Wight OR Islington OR Jersey OR Kensington OR Kent OR Kinross OR Knowsley OR Lambeth OR Lanarkshire OR Lancashire OR Lancaster OR Leeds OR Leicester OR Leicestershire OR Lewisham OR Litchfield OR Lincoln OR Lincolnshire OR Lisburn OR Liverpool OR London OR Londonderry OR Lothian OR Loughborough OR Luton OR Lynn OR Manchester OR Merionnydd OR Merseyside OR Merthyr OR Middlesbrough OR Midlands OR Midlothian OR Monmouth OR Monmouthshire OR Montgomery OR Moray OR Neath OR Newcastle OR Newham OR Newport OR Norfolk OR Northamptonshire OR Northumberland OR Norwich OR Nottingham OR Nottinghamshire OR Orkney OR Oxford OR Oxfordshire OR Pembroke OR Pembrokeshire OR Perth OR Peterborough OR Plymouth OR Pontypridd OR Portsmouth OR Powys OR Preston OR Radnor OR Redbridge OR Renfrewshire OR Rhondda OR Gipon OR Rushmore OR Salford OR Salisbury OR Sandell OR Scarborough OR Scilly OR Sheffield OR Shetland OR Shropshire OR Somerset OR "South Holland" OR Southampton OR Southwark OR Staffordshire OR Stirling OR Stockton OR Stoke OR Suffolk OR Sunderland OR Surrey

OR Sussex OR Swansea OR Talbot OR Tayside OR Thurrock OR Torfaen OR Truro OR Tyne OR Tyneside OR Tyrone OR Wakefield OR Walsall OR Waltham OR Warwickshire OR Wells OR "Western Isles" OR Westminster OR Wiltshire OR Winchester OR Wirral OR Wolverhampton OR Worcester OR Worcestershire OR Wrexham OR "Ynys Mon" OR York OR YorkshireTX Hammersmith OR Hampshire OR Haringey OR Harlow OR Hartlepool OR Harwell OR Helens OR Hereford OR Hertfordshire OR Highland OR Hounslow OR Hull OR Humber OR Inverclyde OR Inverness OR "Isle of Man" OR Wight OR Islington OR Jersey OR Kensington OR Kent OR Kinross OR Knowsley OR Lambeth OR Lanarkshire OR Lancashire OR Lancaster OR Leeds OR Leicester OR Leicestershire OR Lewisham OR Litchfield OR Lincoln OR Lincolnshire OR Lisburn OR Liverpool OR London OR Londonderry OR Lothian OR Loughborough O ...Show Less Search modes - Boolean/Phrase

   View Results (898096)

  S16 TX "Northern Ireland" OR Europe OR British OR Scottish OR Welsh OR International OR "U.K." OR "United Kingdom" OR European OR Britain OR "Channel Isles" OR "Channel Islands" OR Irish OR "EU Member" OR "district council" OR "local council" OR "local authorities" OR "NHS Trust" OR "primary care trust" OR "borough council" OR "county council" OR "local authority" OR "district councils" OR "local councils" OR "NHS Trusts" OR "primary care trusts" OR "borough councils" OR "county councils" OR Eur OR "Social Care Trust" OR Aberdeen OR Aberdeenshire OR "Abertawe Bro Morgan" OR Albans OR Alderney OR "Aneurin Bevan" OR Anglesey OR Angus OR Antrim OR Argyll OR Armagh OR Arran OR Ashfield OR Ayrshire OR Bangor OR Barking OR Bedfordshire OR Belfast OR "Betsi Cadwaladr" OR Bexley OR Birmingham OR Borders OR Bradford OR Brecknock OR Brent OR Bridged OR Brighton OR Bristol OR Buckinghamshire OR Bute OR Caerphilly OR Cambridge OR Cambridgeshire OR Camden OR Cannock OR Canterbury OR Cardiff OR Carlisle OR Carmarthen OR Carmarthenshire OR Ceredigion OR Chelsea OR Cheshire OR Chester OR Chichester OR Clackmannanshire OR Clwyd OR Conway OR Cornwall OR "County Down" OR Coventry OR Croydon OR Cumbria OR "Cwm Taf" OR Cynon OR Dagenham OR Hartford OR Davids OR Denbighshire OR Derby OR Derbyshire OR Devon OR Dorset OR Dudley OR Dumfries OR Dunbartonshire OR Dundee OR Durham OR Ealing OR Edinburgh OR Ely OR Enfield OR Essex OR Exeter OR Falkirk OR Fenland OR Fermanagh OR Fife OR Flintshire OR Forth OR Fulham OR Furness OR Galloway OR Gateshead OR Glamorgan OR Glasgow OR Gloucester OR Gloucestershire OR Grampian OR Gresham OR Greenwich OR Guernsey OR Gwent OR Gwynedd OR Hackney OR Halton OR HamletsTX "Northern Ireland" OR Europe OR British OR Scottish OR Welsh OR International OR "U.K." OR "United Kingdom" OR European OR Britain OR "Channel Isles" OR "Channel Islands" OR Irish OR "EU Member" OR "district council" OR "local council" OR "local authorities" OR "NHS Trust" OR "primary care trust" OR "borough council" OR "county council" OR "local authority" OR "district councils" OR "local councils" OR "NHS Trusts" OR "primary care trusts" OR "borough councils" OR "county councils" OR Eur OR ...Show Less Search modes - Boolean/Phrase

   View Results (1375420)

  S15 TX UK OR Scotland OR England OR Wales OR "national health service" OR NHS OR PCTs OR PCT Search modes - Boolean/Phrase

   View Results (247324)

  S14 S12 NOT S13 Search modes - Boolean/Phrase

   View Results (9436)

  S13 TI (rtpcr OR rtqpcr OR rt-pcr OR rt-qpcr OR "rt pcr" OR "rt qPCR" OR "real time PCR" OR "real-time PCR" OR "real-time qPCR" OR "real time qPCR" OR "real time polymerase chain reaction" OR "real-time polymerase chain reaction" OR "delayed development" OR "developmental delay" OR "likelihood ratio*" OR "predictive value*" OR specificity OR sensitivity) OR AB (rtpcr OR rtqpcr OR rt-pcr

OR rt-qpcr OR "rt pcr" OR "rt qPCR" OR "real time PCR" OR "real-time PCR" OR "real-time qPCR" OR "real time qPCR" OR "real time polymerase chain reaction" OR "real-time polymerase chain reaction" OR "delayed development" OR "developmental delay" OR "likelihood ratio*" OR "predictive value*" OR specificity OR sensitivity)
   View Results (73845)
   S12   S8 NOT S11   Limiters - Published Date from: 20010101-20121231; English; Population Group: Human
Search modes - Boolean/Phrase
   View Results (10358)
   S11   S9 or S10   Search modes - Boolean/Phrase
   View Results (35484)
   S10   DE "Neoplasms" OR DE "Benign Neoplasms" OR DE "Breast Neoplasms" OR DE "Endocrine Neoplasms" OR DE "Leukemias" OR DE "Nervous System Neoplasms" OR DE "Terminal Cancer" OR DE "Benign Neoplasms" OR DE "Breast Neoplasms" OR DE "Endocrine Neoplasms" OR DE "Leukemias" OR DE "Nervous System Neoplasms" OR DE "Brain Neoplasms" OR DE "Glioma" OR DE "Terminal Cancer" OR DE "Oncology"
Search modes - Boolean/Phrase
   View Results (26422)
   S9   TI (neoplas* OR carcinoma* OR cancer* OR malign* OR tumor* OR tumour* OR sarcoma*) OR AB (neoplas* OR carcinoma* OR cancer* OR malign* OR tumor* OR tumour* OR sarcoma*)   Limiters - Published Date from: 20010101-20121231; English
Search modes - Boolean/Phrase
   View Results (24555)
   S8   S5 or S6 or S7   Limiters - Published Date from: 20010101-20121231; English
Search modes - Boolean/Phrase
   View Results (11275)
   S7   S3 and S4   Search modes - Boolean/Phrase
   View Results (11697)
   S6   TI (misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR under-diagnosed OR under-diagnosis under-diagnosis) OR AB (misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR under-diagnosed OR under-diagnosis under-diagnosis)   Search modes - Boolean/Phrase
   S5   DE "Misdiagnosis" OR MJ "Early Intervention"   Search modes - Boolean/Phrase
   View Results (6241)
   S4   TI (late OR later OR early OR earlier OR error OR errors OR wrong OR wrongly OR correct OR correctly OR incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR rapid) OR TI (delay OR delays OR delaying OR delayed) OR AB (delay OR delays OR delaying OR delayed)   Search modes - Boolean/Phrase
   View Results (137903)
   S3   S1 or S2   Search modes - Boolean/Phrase
   View Results (216661)
   S2   TI (detect OR detection OR detecting OR "help seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present) OR TI (diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic) OR AB (diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic)   Search modes - Boolean/Phrase
   View Results (205814)
   S1   DE "Differential Diagnosis" OR DE "Medical Diagnosis" OR DE "Diagnosis" OR DE "Prenatal Diagnosis" OR DE "Screening"   Search modes - Boolean/Phrase
   View Results (43772)

02.11.11

No.	Database	Search term	Hits
23	PsycINFO	(systematic AND review).ti,ab	10192
24	PsycINFO	(detect OR detection OR detecting OR "help seeking" OR "help-seeking" OR help-seeking OR referred OR referral OR referrals OR presentation OR presenting OR present).ti	26962
25	PsycINFO	(diagnosis OR diagnose OR diagnosed OR diagnosing OR diagnoses OR diagnostic).ti,ab	180407
27	PsycINFO	DIAGNOSIS/ OR DIFFERENTIAL DIAGNOSIS/ OR MEDICAL DIAGNOSIS [+NT]/ OR PSYCHODIAGNOSIS [+NT]/ OR DUAL DIAGNOSIS/ OR SCREENING [+NT]/	62707
28	PsycINFO	MISDIAGNOSIS/	332
29	PsycINFO	(misdiagnosis OR misdiagnoses OR mis-diagnosis OR mis-diagnoses OR misdiagnosed OR mis-diagnosed OR undiagnosed OR underdiagnosed OR under-diagnosed OR under-diagnosis OR underdiagnose OR under-diagnose OR misdiagnose OR mis-diagnose).ti,ab	3589
30	PsycINFO	TIME/	9529
31	PsycINFO	(late OR later OR early OR earlier OR error OR errors OR wrong OR wrongly OR correct OR correctly OR incorrect OR incorrectly OR missed OR missing OR miss OR mistake OR mistakes OR mistaken OR mistakenly OR time OR timely OR untimely OR rapid).ti	90951
32	PsycINFO	(delay OR delays OR delaying OR delayed).ti,ab	48202
33	PsycINFO	exp NEOPLASMS/	26393
34	PsycINFO	(neoplas* OR cancer* OR tumor* OR tumour* OR sarcom* OR carcinoma* OR maligna*).ti,ab	38920
35	PsycINFO	24 OR 25 OR 27	221423
36	PsycINFO	30 OR 31 OR 32	139811
37	PsycINFO	35 AND 36	11832
38	PsycINFO	28 OR 29	3719
39	PsycINFO	37 OR 38	15301
40	PsycINFO	33 OR 34	41061
41	PsycINFO	39 NOT 40	14491
42	PsycINFO	23 AND 41	81
43	PsycINFO	39 NOT 40 [Limit to: Publication Year 2001-2012 and (Languages English)]	8056
44	PsycINFO	23 AND 41 [Limit to: Publication Year 2001-2012 and	65

PUBMED
Searched 25.10.11/02.11.11

(((((((((mass screening[MeSH Major Topic] OR "diagnosis"[mh:noexp] OR diagnosis, differential[MeSH Major Topic] OR diagnostic errors[MeSH Major Topic] OR

incidental findings[MeSH Major Topic] OR "prenatal diagnosis"[mh:noexp] OR detect[Ti] OR detection[Ti] OR detecting[Ti] OR "help seeking"[Ti] OR help-seeking[Ti] OR referred[Ti] OR referral[Ti] OR referrals[Ti] OR presentation[Ti] OR presenting[Ti] OR present[Ti] OR diagnosis[tiab] OR diagnose[tiab] OR diagnosed[tiab] OR diagnosing[tiab] OR diagnoses[tiab] OR diagnostic[tiab]) AND (delay[tiab] OR delays[tiab] OR delaying[tiab] OR delayed[tiab] OR time factors[MeSH Major Topic] OR late[ti] OR later[ti] OR early[ti] OR earlier[ti] OR error[ti] OR errors[ti] OR wrong[ti] OR wrongly[ti] OR correct[ti] OR correctly[ti] OR incorrect[ti] OR incorrectly[ti] OR missed[ti] OR missing[ti] OR miss[ti] OR mistake[ti] OR mistakes[ti] OR mistaken[ti] OR mistakenly[ti] OR time[ti] OR timely[ti] OR untimely[ti] OR rapid[ti])) OR (delayed diagnosis[MeSH Terms] OR early diagnosis[mh:noexp] OR misdiagnosis[tiab] OR misdiagnoses[tiab] OR mis-diagnosis[tiab] OR mis-diagnoses[tiab] OR misdiagnosed[tiab] OR mis-diagnosed[tiab] OR undiagnosed[tiab] OR underdiagnosed[tiab] OR under-diagnosed[tiab] OR under-diagnosis[tiab] OR under-diagnosis[tiab])) AND (((Northern Ireland[PL]) OR (United Kingdom[PL]) OR (Britain[PL]) OR (Scotland[PL]) OR (Wales[PL]) OR (England[PL]) OR (great britain[MeSH Terms] OR (europe[MeSH Terms:noexp]) OR (Northern Ireland[MeSH Terms]) OR UK OR Scotland OR England OR Wales OR "Northern Ireland" OR Europe OR British OR Scottish OR Welsh OR International OR U.K. OR "United Kingdom" OR European OR Britain OR "Channel Isles" OR "Channel Islands" OR English[tiab] OR Irish OR "EU Member"[tiab] OR "district council" OR "local council" OR "local authorities" OR "NHS Trust" OR "primary care trust" OR "borough council" OR "county council" OR "local authority" OR "district councils" OR "local councils" OR "NHS Trusts" OR "primary care trusts" OR "national health service" OR NHS OR PCTs OR PCT OR "borough councils" OR "county councils" OR Eur OR "Social Care Trust" OR Aberdeen OR Aberdeenshire OR "Abertawe Bro Morgannwg" OR Albans OR Alderney[tiab] OR "Aneurin Bevan" OR Anglesey OR Angus OR Antrim OR Argyll OR Armagh OR Arran OR Ashfield OR Ayrshire OR Bangor OR Barking OR Bath[tiab] OR Bedfordshire OR Belfast OR "Betsi Cadwaladr" OR Bexley OR Birmingham OR Borders OR Bradford OR Brecknock OR Brent OR Bridgend OR Brighton OR Bristol OR Buckinghamshire OR Bute OR Caerphilly OR Cambridge OR Cambridgeshire OR Camden OR Cannock OR Canterbury OR Cardiff OR Carlisle OR Carmarthen OR Carmarthenshire OR Ceredigion OR Chelsea OR Cheshire OR Chester OR Chichester OR Clackmannanshire OR Clwyd OR Conwy OR Cornwall OR "County Down" OR Coventry OR Croydon OR Cumbria OR "Cwm Taf" OR Cynon OR Dagenham OR Dartford OR Davids OR Denbighshire OR Derby OR Derbyshire OR Devon OR Dorset OR Dudley OR Dumfries OR Dunbartonshire OR Dundee OR Durham OR Ealing OR Edinburgh OR Ely OR Enfield OR Essex OR Exeter OR Falkirk OR Fenland OR Fermanagh OR Fife OR Flintshire OR Forth OR Fulham OR Furness OR Galloway OR Gateshead OR Glamorgan OR Glasgow OR Gloucester OR Gloucestershire OR Grampian OR Gravesham OR Greenwich OR Guernsey OR Gwent OR Gwynedd OR Hackney OR Halton OR Hamlets OR Hammersmith OR Hampshire[tiab] OR Haringey OR Harlow OR Hartlepool OR Harwell OR Helens OR Hereford OR Hertfordshire OR Highland OR Hounslow OR Hull OR Humber OR Inverclyde OR Inverness OR "Isle of Man" OR Wight OR Islington OR Jersey[tiab] OR Kensington OR Kent OR Kinross OR Knowsley OR Lambeth OR Lanarkshire OR Lancashire OR Lancaster OR Leeds OR Leicester OR

Leicestershire OR Lewisham OR Lichfield OR Lincoln OR Lincolnshire OR Lisburn OR Liverpool OR London OR Londonderry OR Lothian OR Loughborough OR Luton OR Lynn OR Manchester OR Meirionnydd OR Merseyside OR Merthyr OR Middlesbrough OR Midlands OR Midlothian OR Monmouth OR Monmouthshire OR Montgomery OR Moray OR Neath OR Newcastle OR Newham OR Newport[tiab] OR Norfolk OR Northamptonshire OR Northumberland OR Norwich OR Nottingham OR Nottinghamshire OR Orkney OR Oxford OR Oxfordshire OR Pembroke OR Pembrokeshire OR Perth OR Peterborough OR Plymouth OR Pontypridd OR Portsmouth OR Powys OR Preston OR Radnor OR Redbridge OR Renfrewshire OR Rhondda OR Ripon OR Rushmoor OR Salford OR Salisbury OR Sandwell OR Scarborough OR Scilly OR Sheffield OR Shetland OR Shropshire OR Somerset OR "South Holland" OR Southampton OR Southwark OR Staffordshire OR Stirling OR Stockton OR Stoke OR Suffolk OR Sunderland OR Surrey OR Sussex OR Swansea OR Talbot OR Tayside OR Thurrock OR Torfaen OR Truro OR Tyne OR Tyneside OR Tyrone OR Wakefield OR Walsall OR Waltham OR Warwickshire OR Wells OR "Western Isles" OR Westminster OR Wiltshire OR Winchester OR Wirral OR Wolverhampton OR Worcester OR Worcestershire OR Wrexham OR "Ynys Mon" OR York OR Yorkshire)) NOT ("New Jersey" OR Alabama OR Ontario OR "New London" OR "New England" OR "New South Wales" OR "New York"))) NOT ((Animals[mh]) NOT (Animals[mh] AND Humans[mh]))) NOT (cancer[sb])) NOT (rtpcr OR rtqpcr OR rt-pcr OR rt-qpcr OR "rt pcr" OR "rt qPCR" OR "real time PCR" OR "real-time PCR" OR "real-time qPCR" OR "real time qPCR" OR "real time polymerase chain reaction" OR "real-time polymerase chain reaction" OR "Nucleic Acid Amplification Techniques"[mh] OR "delayed development" OR "developmental delay" OR "predictive value" OR "predictive values" OR "likelihood ratio" OR "likelihood ratios" OR specificity OR sensitivity OR "Sensitivity and Specificity"[mh]) AND (2001 : 2012[dp])) AND (English[LA])

OR

Search: ((((((mass screening[MeSH Major Topic] OR "diagnosis"[mh] OR diagnosis, differential[MeSH Major Topic] OR diagnostic errors[MeSH Major Topic] OR incidental findings[MeSH Major Topic] OR "prenatal diagnosis"[mh] OR detect[Ti] OR detection[Ti] OR detecting[Ti] OR "help seeking"[Ti] OR help-seeking[Ti] OR referred[Ti] OR referral[Ti] OR referrals[Ti] OR presentation[Ti] OR presenting[Ti] OR present[Ti] OR diagnosis[tiab] OR diagnose[tiab] OR diagnosed[tiab] OR diagnosing[tiab] OR diagnoses[tiab] OR diagnostic[tiab]) AND (delay[tiab] OR delays[tiab] OR delaying[tiab] OR delayed[tiab] OR time factors[MeSH Major Topic] OR late[ti] OR later[ti] OR early[ti] OR earlier[ti] OR error[ti] OR errors[ti] OR wrong[ti] OR wrongly[ti] OR correct[ti] OR correctly[ti] OR incorrect[ti] OR incorrectly[ti] OR missed[ti] OR missing[ti] OR miss[ti] OR mistake[ti] OR mistakes[ti] OR mistaken[ti] OR mistakenly[ti] OR time[ti] OR timely[ti] OR untimely[ti] OR rapid[ti])) OR (delayed diagnosis[MeSH Terms] OR early diagnosis[mh] OR misdiagnosis[tiab] OR misdiagnoses[tiab] OR mis-diagnosis[tiab] OR mis-diagnoses[tiab] OR misdiagnosed[tiab] OR mis-diagnosed[tiab] OR undiagnosed[tiab] OR underdiagnosed[tiab] OR under-diagnosed[tiab] OR under-diagnosis[tiab] OR under-diagnosis[tiab])) NOT ((Animals[mh]) NOT (Animals[mh] AND Humans[mh]))) NOT (cancer[sb])) NOT (rtpcr OR rt pcr OR rt-pcr OR rt-qpcr OR

"rt pcr" OR "rt qPCR" OR "real time PCR" OR "real-time PCR" OR "real-time qPCR" OR "real time qPCR" OR "real time polymerase chain reaction" OR "real-time polymerase chain reaction" OR "Nucleic Acid Amplification Techniques"[mh] OR "delayed development" OR "developmental delay" OR "predictive value" OR "predictive values" OR "likelihood ratio" OR "likelihood ratios" OR specificity OR sensitivity OR "Sensitivity and Specificity"[mh])) AND and AND (systematic review[Title/Abstract] AND (English[lang] AND "last 10 years"[PDat]))

 OR

("early intervention" AND "systematic review" Limits: Humans, English, published in the last 10 years NOT cancer[sb])

Appendix 2: Quality Appraisal Tools

A2.1 AMSTAR QUALITY APPRAISAL TOOL

1 Was an ''a priori'' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

2 Was there duplicate study selection and data extraction?
Duplicate coding must have been carried out for study selection and data extraction. Were there at least two independent data extractors and a consensus procedure for disagreements in place?

3 Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms should be stated, and where feasible, the search strategy should be provided.

4 Was the status of publication (i.e., grey literature) used as an inclusion criterion?
The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

5 Was a list of studies (included and excluded) provided?
Is there a flow of studies diagram? A list of included and excluded studies should be provided.

6 Were the characteristics of the included studies provided?
In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes.

7 Was the scientific quality of the included studies assessed and documented?
Was a quality assessment tool used to appraise studies? ''A priori'' methods of assessment should be provided.

8 Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality assessment should be considered in the analysis and the conclusions of the review, and where there are recommendations, explicitly stated in their formulation.

9 Were the methods used to combine the findings of studies appropriate?
Narrative synthesis is appropriate where studies are qualitative/ heterogeneous. For pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity. If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration.

10 Was the likelihood of publication bias assessed?
Where appropriate, an assessment of publication bias should include a combination of graphical aids and/or statistical tests.

11 Was conflict of interest reported?
Potential sources of support should be clearly acknowledged.

A2.2 QATSO QUALITY ASSESSMENT TOOL

1.Was the sampling method appropriate / was the sample representative of the population under study?

Is the method: probability sampling including: simple random / systematic / stratified / cluster / two-stage / multi-stage sampling (score 1) or non-probability sampling including: Including: purposive / quota / convenience / snowball sampling (score0)?

2.Was the measurement of the independent variable(s) likely to be reliably assessed and validated?
Reliability pointers: Do authors describe how the information was collected? Do they describe ways they tried to ensure it was consistently collected? Was data collection piloted? Were data collection tools previously developed or tested? Was data collection tape recorded and/or transcribed? Validity pointers: Do authors describe why they collected the information they did? Does it fit with the study's aims? Was the information they collected what you would consider to be important to answer their research question? Do they mention previous validation of tools? Were previously piloted/developed tools used? Was the target population involved in development of the tools? Did researchers use more than one method of data collection?

3.Dependent variable(s) reliable/valid measurement?

4.Did the study report any response rate?
If the reported response rate is below 60%, the question should be answered 'no'

5.Did the investigator(s) control for confounding factors in analysing the associations?
e.g. stratification / matching / restriction / adjustment

6.Do you have any concerns about the statistical methods used?

7.Was follow-up long enough for the outcomes to occur?

8. What is the overall grade of the study?
1-3 = LOW QUALITY, 4-6 = MEDIUM QUALITY, 7 = HIGH QUALITY

9. Overall how relevant is the study for this review?

A2.3 QUALITY ASSESSMENT TOOL FOR COMPARISON GROUP STUDIES

1. Methodological characteristics of the study
1.1 Number of participants recruited to intervention and control/comparison groups
1.2 What was the unit of allocation into each intervention and control/comparison group?
1.3 Was the allocation to intervention and control/ comparison groups done blind?
1.4 Were participants aware which group they were in for the evaluation?
1.5 Was outcome measurement done blind?
1.6 What sort of measurement tool(s) is/are used to collect outcome data?
1.7 Name of measuring tools
1.8 Were the measuring tools validated?
1.9 Number of outcome assessment periods
1.10 Timing(s) of post-intervention measurements
1.11 Did the study use 'intention-to-treat' or 'Intervention received' analysis method?
2. Avoiding selection bias
2.1How were subjects allocated to control and intervention groups? Random/non random
2.2 Did the analysis adjust for baseline imbalances in major prognostic factors between groups?
3.Avoiding attrition bias
3.1 Is the attrition rate reported separately according to allocation group?
3.2 What is the attrition rate?
4.Avoiding selective reporting bias
4.1 What outcomes did the authors say they were intending to measure (i.e. as described in the aims of the evaluation?)
4.2 For whom were outcomes given?
5.Decision on soundness of study
5.1 Was selection bias avoided?
5.2 Was attrition bias avoided?
5.3 Was selective reporting bias avoided
6.Taking account of the above, what is the weight of evidence A?
High trustworthiness, medium trustworthiness, low trustworthiness
7.Weight of evidence B: Appropriateness of research design and analysis for addressing the questions of this review
High, Medium, Low
8.Weight of evidence C: Relevance of particular focus of the study (including conceptual focus, context, sample and measures) for addressing the question of the review
High, Medium, Low
9.Weight of evidence D: Overall weight of evidence **High, Medium, low**

A2.4 QUALITY ASSESSMENT FOR QUALITATIVE STUDIES

1. Were steps taken to strengthen rigour in the sampling?
1.1 Yes, a fairly thorough attempt was made - Score 3
1.2 Yes, several steps were taken - Score 2
1.3 Yes, minimal few steps were taken - Score 1
1.4 Unclear - Score 0
1.5 No, not at all / Not stated / Can't tell - Score 0
2. Were steps taken to strengthen rigour in the data collected?
2.1 Yes, a fairly thorough attempt was made - Score 3
2.2 Yes several steps were taken - Score 2
2.3 Yes, minimal few steps were taken - Score 1
2.4 Unclear - Score 0
2.5 No, not at all / Not stated / Can't tell - Score 0
3. Were steps taken to strengthen the rigour of the analysis of data?
3.1 Yes, a fairly thorough attempt was made - Score 3
3.2 Yes, several steps were taken - Score 2
3.3 Yes, minimal steps were taken - Score 1
3.4 Unclear - Score 0
3.5 No, not at all / Not stated / Can't tell - Score 0
4. Were the findings of the study grounded in / supported by the data?
4.1 Well grounded / supported - Score 3
4.2 Fairly well grounded / supported - Score 2
4.3 Limited grounding / support - Score 1
5. Please rate the findings of the study in terms of their breadth and depth
5.1 Good / Fair breadth, but little depth - Score 2
5.2 Good / fair depth but very little breadth - Score 2
5.3 Good / fair breadth and depth - Score 3
5.4 Limited breadth and depth - Score 1
6. Privileges participants' perspectives/experiences?
6.1 Not at all - Score 0
6.2 A little - Score 1
6.3 Somewhat - Score 2
6.4 A lot - Score 3

Overall grade for the qualitative study: High Quality:17-18; Medium Quality: 9-16; Low Quality: 1-8.

Appendix 3: Systematic Map

Section 1

This section covers a breakdown of:

- Types of conditions
- Date of publication
- Study Design
- Number of patients
- Type of delay

Types of condition

Systematic reviews

Condition / Disease	No. of Studies
Dementia (Alzheimers)	3
Depression	3
Diabetes Type 1	1
Epilepsy	2
HIV	2
Kidney disease (acute, chronic) renal failure	5
Myocardial infarction	5
Psychosis - schizophrenia, bipolar disorder	5
Stroke	5
Tuberculosis	4

Studies looking at multiple conditions
Missed test results for hospital patients
15 common chronic diseases leading to disability
Help seeking behaviour of men
Patients presenting to primary care
General health conditions
Acutely unwell ward patients
Autopsy detected diagnostic errors
Test ordering by doctors during diagnosis
Thrombolysis administration by nurses

Primary Studies

Condition / Disease	No. of studies
Chronic Obstructive Pulmonary Disease	12

Date of publication

Systematic Reviews

Year	Count
2002	1
2003	1
2004	2
2005	3
2006	3
2007	3
2008	6
2009	4
2010	11
2011	8

Primary Studies: COPD

Year	Count
2001	1
2004	1
2006	4
2007	1
2008	1
2010	3
2011	1

Type of Study Design

In the systematic reviews, the study design relates to the type of studies included in the review.

Type of Study Design
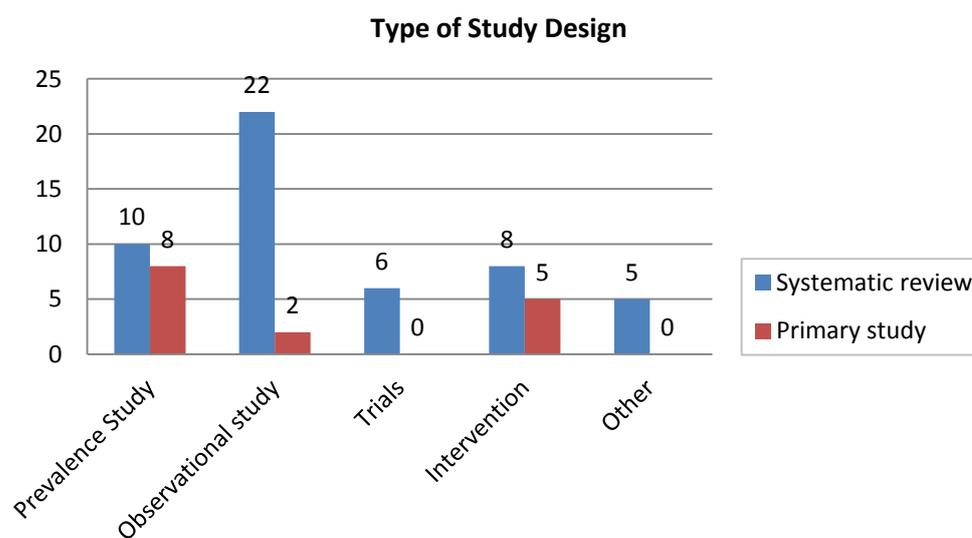
Number of patients

Systematic Reviews

Condition	Study	Type of Studies included in Review	No. of patients
Dementia	Bradford et al. 2009	Prevalence Qualitative	2,160 For the accuracy of diagnosis studies.
	Koch et al. 2010	Observational Qualitative Mixed methods	Not stated
	Koch and Iliffe 2011	Trials	3,172
Depression	Cepiou et al. 2008	Prevalence	60,494
	Das et al. 2006	Observational study	59,758
	Mitchell et al. 2007	Prevalence	35,980
Diabetes Type 1	Usher-Smith 2011	Observational	24,000 children
Epilepsy	Chapman et al. 2010	Prevalence	1,363 children and adults
	Juarez-Garcia et al. 2006	Prevalence with costs of misdiagnosis included	835
HIV	Chen et al. 2011	Prevalence Observational	Late diagnosis studies - 391,970 Survival after diagnosis - 975,327
	Deblonde et al. 2010	Observational	30,368 patients 38,170 consultation records
Kidney Disease	Black et al. 2010	Cohort studies	114,073 effectiveness studies 16,600 outcome studies
	Chan et al. 2007	Cohort studies	12,749
	Kahn and Ameida 2008	Unclear	Not stated
	Navaneethan et al. 2008	Cohort studies Surveys	10,115
	Smart and Titus 2011	Cohort studies Database analysis	17,646

Condition	Study	Type of Studies included in Review	No. of patients
Myocardial infarction	Brainard et al. 2005	Observational	99
	Centre for Reviews and Dissemination 2004	Observational Intervention	Predictor studies - 12,207 Intervention studies - 15,459
	Dubayova et al. 2010	Qualitative	1,634 AMI patients
	Herlitz et al. 2010	Observational	AMI/ACS patients - 4,543
	McManus et al. 2002	Trials	not stated
Psychosis	Farooq et al. 2009	Observational	1,681
	Lloyd Evans et al. 2010	Interventions	Not stated
	Marshall et al. 2006	Observational	4,490
	Perkins et al. 2005	Observational	Review and Meta-Analysis of the Relationship Between Duration of Untreated Psychosis and Outcome in First-Episode Schizophrenia: 5,501 patients

Studies Examining the Relationship Between Duration of Untreated Psychosis and Treatment Response - baseline only: 1,915 patients |
Stroke	Herlitz et al. 2010	Observational	Stroke patients - 31,135
	Jones et al. 2010	Observational	public and patients: 143,191
	Kwan et al. 2004	Intervention	6,345
	Lecouturier et al. 2010	Survey Review of documentation Qualitative	5,765
	Lecouturier et al. 2010	Intervention	Not stated

Condition	Study	Type of Studies included in Review	No. of patients
Tuberculosis	Courtwright and Turner 2010	Observational	Not stated
	Liu et al. 2008	Intervention / trials	4,089 for diagnosis studies
	Sreeramareddy et al. 2009	Prevalence	Not reported
	Storla et al. 2008	Prevalence / observational	Not reported
Miscellaneous	Callen et al. 2011	Prevalence/ Observational	5,314 patients. Numbers of patients not recorded for all studies.
	Falagas et al. 2007	Prevalence	Not stated
	Galdas et al. 2005	Observational Qualitative	Not stated
	Kostopoulou et al. 2008	Observational	4,524 patients - excluding cancer patients.
	Main et al. 2010	Trials	Not stated
	Quirke et al. 2011	Observational	Not stated
	Shojania et al. 2003	Prevalence / observational	13,260
	Sloman et al. 2009	Trials	91
	Whiting et al. 2007	Observational	Not stated

Primary Studies: COPD

Study	Type of Study	No. of Patients
Bastin et al. 2010	Case review Cross sectional study	41
Bolton et al. 2004	Evaluation Case review Cross sectional study	Not stated
Calderon Larranaga et al. 2010	Secondary analysis	53,676,051
Frank et al. 2006	Case finding	825
Hassett et al. 2006	Evaluation	364
Jones et al. 2008	Case review Cross-sectional study	632
Jordan et al. 2010	Modelling	20,496
Nacul et al. 2010	Modelling	Not stated
Seamark et al. 2001	Evaluation	127
Shahab et al. 2006	Secondary analysis	8,215
Tinkelman et al. 2007	Case finding Cross-sectional study	818
Walker et al. 2006	Case Review Cross-sectional study	1,508

Types of Delay

We used Hansen's model of diagnostic delay (Hansen et al. 2008) to code.

Type of Delay
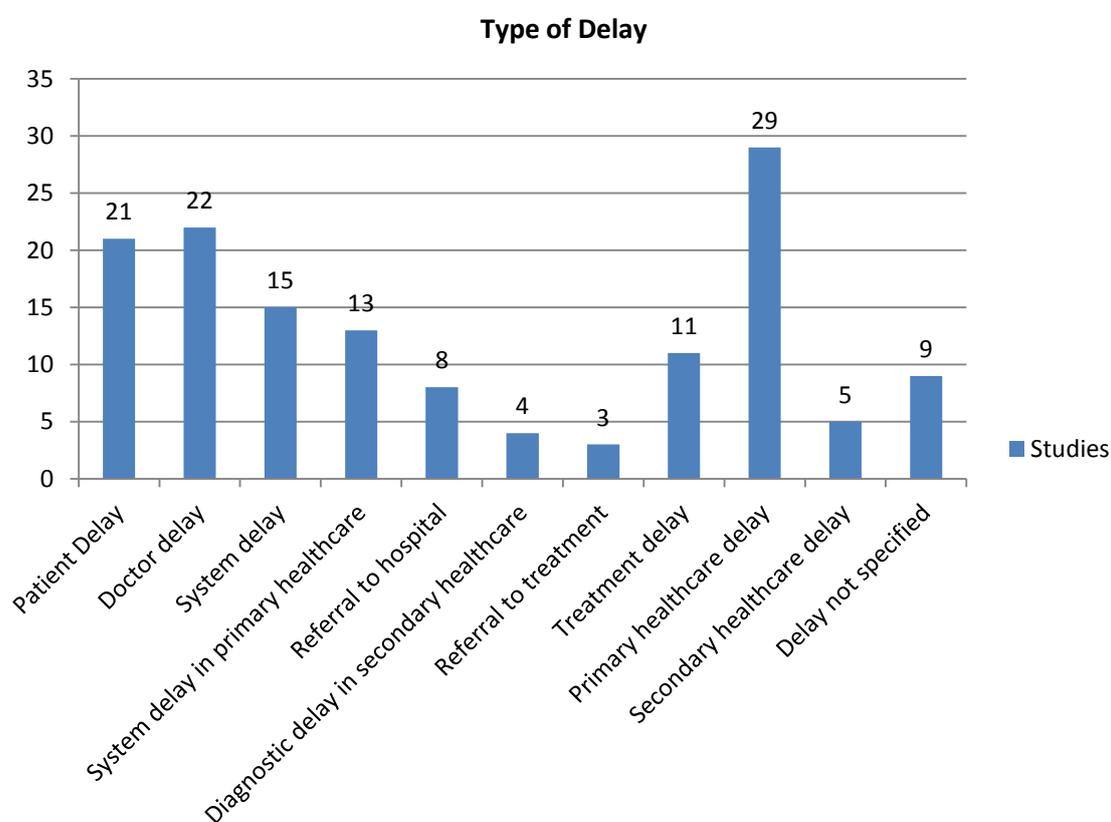
Section 2: Study Response to Research Questions

Under each of the potential review questions we list studies that could address that question. All of the studies are systematic reviews, except those investigating COPD. Some studies look at more than one condition and these have some additional description to give a better understanding of what they might cover.

1 What is the prevalence of late diagnosis? (n=19)

Study	Conditions
Bradford et al. 2009	Dementia
Calderon et al. 2010	COPD
Callen et al. 2011	Multiple conditions: missed test results
Cepiou et al. 2008	Depression
Chapman et al. 2010	Epilepsy
Chen et al. 2011	HIV
Falagas et al. 2007	Multiple conditions: common chronic diseases
Frank et al. 2006	COPD
Jordan et al. 2010	COPD
Juarez-Garcia et al. 2006	Epilepsy

Study	Conditions
Kahn and Amedia 2008	Kidney Disease
Mitchell et al. 2011	Mild distress/depression
Nacul et al. 2011	COPD
Shojania et al. 2003	Multiple conditions: autopsy detected diagnostic errors
Sreeramareddy et al. 2009	Tuberculosis
Storla et al. 2005	Tuberculosis
Tinkelman et al. 2007	COPD
Walker et al. 2006	COPD
Usher Smith et al. 2011	Type 1 Diabetes

2 What are the determinants of late diagnosis?

Demographic Determinants (n=14)

Study	Conditions	Type of Demographic Determinant
Black et al. 2010	Kidney disease	Age, Ethnicity
Bradford et al. 2009	Dementia	Gender
Calderon et al. 2010	COPD	Socio economic status
Chen et al. 2011	HIV	Gender, ethnicity, foreign born
Cepiou et al. 2008	Depression	Age
Das et al. 2006	Depression	Ethnicity
Galdas et al. 2005	Multiple conditions: help seeking behaviour	Gender, socio economic status, ethnicity
Herlitz et al. 2010	Myocardial infarction / stroke	Gender
Jones et al. 2010	Stroke	Age, level of education, ethnicity
Jordan et al. 2010	COPD	Gender
Nacul et al. 2011	COPD	North south divide, urban areas
Navaneethan et al. 2008	Kidney disease	Age, socio economic status, level of education, ethnicity
Storla et al. 2008	Tuberculosis	Age, gender, socio economic status, level of education, rural residence, low access (geographical or socio psychological barriers), history of immigration
Usher Smith et al. 2011	Type 1 Diabetes	Age, socio economic status, level of education, ethnicity.

Medical Determinants of Delay (n=13)

Study	Conditions	Type of medical determinants
Black et al. 2010	Kidney disease	Co-morbidities, non specific presentation
Bradford et al. 2009	Dementia	Disease severity, patient impairment, dementia sub type
Chapman et al. 2010	Epilepsy	Co-morbidities, misinterpretation of behavioural, physiological, syndrome related, medication related or psychological events
Das et al. 2006	Depression	Co-morbidities, depression, atypical presentation
Glazer et al. 2008	Tracheobronchial injuries	Non specific presentation
Koch et al. 2010	Dementia	Non specific presentation
Kostopoulou et al. 2008	Multiple conditions: diagnostic error in primary care	Co-morbidities, atypical presentation, non specific presentation, rarity of condition
McManus et al. 2001	Acute coronary syndrome	Atypical presentation
Mitchell et al. 2011	Distress/ depression	Disease severity
Navaneethan et al. 2008	Kidney disease	Co-morbidities
Quirke et al. 2011	Multiple conditions: acutely unwell ward patients	Co-morbidities
Storla et al. 2008	Tuberculosis	Co-morbidities, atypical presentation
Usher Smith et al. 2011	Type 1 Diabetes	Co-morbidities, preceding infection, low BMI

System Determinants of Delay (n=12)

Study	Condition	Type of system determinants
Black et al. 2010	Kidney disease	Referral strategies
Bradford et al. 2009	Dementia	Access to care
Callen et al. 2011	Multiple conditions: missed test results	Patients moving across health care settings, failure to follow up test results
Das et al. 2006	Depression	Access to care
Deblonde et al. 2010	HIV	Access to care, system resource contraints
Herlitz et al. 2010	Myocardial infarction	Referral strategies, system resource contraints
Koch et al. 2010	Dementia	System resource contraints, pressure on time
McManus et al. 2001	Acute coronary syndrome	Specialised services
Navaneethan et al. 2008	Kidney disease	Access to care, specialised services, patients moving across healthcare settings, physicians knowledge

Study	Condition	Type of system determinants
Quirke et al. 2011	Multiple conditions: acutely unwell ward patients	System resource constraints
Sreeramareddy et al. 2009	Tuberculosis	Healthcare system delays (not further specified)
Storla et al. 2008	Tuberculosis	Access to care

Other Determinants of Delay (n=13)

Study	Condition	Type of determinant
Bradford et al. 2009	Dementia	Patient / provider communication
Courtwright and Turner 2010	Tuberculosis	Patient attitudes: stigma
Das et al. 2006	Depression	Patient attitudes: stigma Patient / provider communication
Deblonde et al. 2010	HIV	Patient beliefs and attitudes: low risk perception, fears and worries Patient / provider communication
Dubayova et al. 2010	Myocardial infarction	Patient attitudes: fear
Galdas et al. 2005	Multiple conditions: help seeking behaviour	Patient knowledge, beliefs and attitudes
Herlitz et al. 2010	Myocardial infarction / stroke	Patients knowledge, beliefs and attitudes
Jones et al. 2010	Stroke	Patients knowledge, beliefs and attitudes
Koch et al. 2010	Dementia	Patient attitudes: stigma Patient / provider communication
Lecouturier et al. 2010	Stroke	Patient knowledge
Lecouturier et al. 2010b	Stroke	Patient knowledge
Storla et al. 2008	Tuberculosis	Patients knowledge, beliefs and attitudes

3 What are the outcomes of late diagnosis?

Types of Outcomes Excluding Cost (n=15)

Study	Conditions	Type of Outcome
Bastin et al. 2010	COPD	Morbidity
Black et al. 2010	Kidney disease	Mortality, hospitalization, treatment
Chan et al. 2007	Kidney disease	Resource implications, morbidity, mortality
Chen et al. 2011	HIV	Morbidity, mortality
Dubayova et al. 2010	Myocardial infarction	Time to first consultation,
Falagas et al. 2007	Multiple conditions: common chronic diseases	Morbidity, mortality
Farooq et al. 2009	Psychosis	Morbidity, mortality
Glazer et al. 2008	Tracheobronchial injuries	Time to diagnosis
Herlitz et al. 2010	Myocardial infarction / stroke	Time to presentation
Kahn and Amedia 2008	Kidney disease	Mortality, hospitalization, treatment
Lecouturier et al. 2010b	Stroke	Time to presentation
Perkins et al. 2005	Psychosis	Morbidity, greater response to treatment
Smart et al. 2011	Kidney disease	Resource implications, morbidity, mortality
Sreeramareddy et al. 2009	Tuberculosis	Morbidity, mortality, transmission
Usher Smith et al. 2011	Type 1 Diabetes	Morbidity

4 What are the cost implications of late diagnosis? (n=3)

Study	Condition
Black et al. 2010	Kidney disease
Juarez-Garcia et al. 2006	Epilepsy
Khan and Amedia 2008	Kidney disease

5 Which interventions reduce delays in diagnosis? (n=15)

Study	Conditions	Type of intervention	Type of Outcome measured
Black et al. 2010	Kidney disease	Early referral strategies	Cost Resource implications, morbidity, quality of life, mortality
Centre for Reviews 2004	Myocardial infarction	Community interventions	Resource implications, reduced time delay
Hassett et al. 2006	COPD	Specialist unit	Accuracy of diagnosis, patient and GP satisfaction
Jordan et al. 2010	COPD	Case finding	New cases
Koch et al. 2011	Dementia	Doctors education, service redesign	Increased knowledge, resource implications, quality of life, stakeholder satisfaction, care delivered according to guidelines
Kwan et al. 2004	Stroke	Mass media campaign, doctors education, helicopter transfer of patients to hospital, re-organization of in-hospital systems to streamline acute stroke care.	Time to admission / treatment
Lecouturier et al. 2010	Stroke	Mass media campaign, doctors education	Time to presentation
Liu et al. 2008	Tuberculosis	Reminder systems and late patient tracers	Completion of diagnostics
Lloyd Evans et al. 2011	Psychosis	Mass media campaign, doctors education, multi focus initiatives, early intervention services.	Time to diagnosis
Main et al. 2010	Multiple conditions	Diagnostic decision support systems	Cost Resource implications, practitioner performance

Study	Conditions	Type of intervention	Type of Outcome measured
McManus et al. 2002	Acute coronary syndrome	Specialist units	Time to diagnosis, admission rate to hospital, detection rate of syndrome unrecognised by GPs, timing of specialist assessment, speed and accuracy of detection of those with non-cardiac chest pain.
Sloman et al. 2009	Myocardial infarction	Thrombolysis administration by nurses	Time to diagnosis, accuracy of diagnosis
Smart and Titus 2011	Kidney disease	Referral to specialist care versus standard care	Mortality, hospitalization, type of dialysis.
Tinkelman et al. 2007	COPD	At risk groups screening	New cases
Walker et al. 2006	COPD	At risk groups screening	Morbidity, new cases, better treatment and management

Appendix 4 Quality of the included studies

Table A4.1: Systematic Reviews – Quality Assessment

Study	1. A priori design	2. Duplicate study selection and extraction	3. Comprehensive literature review	4. Status of publication as inclusion criteria	5. List of studies (excluded and included)	6. Characteristics of studies	7. Scientific quality assessed	8. Scientific quality used in conclusions	9. Methods to combine findings appropriate	10. Publication bias assessed	11. Conflict of interest reported	3,6 and 7 apply	Overall score
Anderson et al. 2010	√	√	√	√	√	√	√	√	√	x	√	Yes	10
Bird et al. 2010	√	x	√	x	√	√	√	√	√	x	√	Yes	8
Black et al. 2010	√	√	√	√	√	√	√	√	√	x	√	Yes	10
Boersma et al. 2006	√	x	√	√	√	√	√	√	√	√	√	Yes	10
Bradford et al. 2009	√	x	√	√	√	√	x	x	√	√	√	No	8
Brainard et al. 2005	√	√	√	√	√	x	√	√	√	√	x	No	9
*Callen et al. 2011	√	√	√	√	√	√	x	x	√	√	√	No	9
Cepiou et al. 2008	√	x	√	√	√	√	√	√	√	x	√	Yes	9
Chan et al. 2007	√	√	√	√	√	√	√	√	√	√	x	Yes	10
Chapman et al. 2010	√	√	√	√	√	√	√	√	√	x	√	Yes	10
Chen et al. 2011	x	x	x	√	√	√	x	x	√	x	x	No	4
Courtwright and Turner 2010	√	x	x	√	√	x	x	x	√	√	x	No	5
Das et al. 2006	√	x	x	x	x	√	x	x	√	x	√	No	4
De Luca et al. 2008	√	x	√	√	√	√	√	√	√	√	√	Yes	10
Deblonde et al. 2010	√	x	√	√	√	√	x	x	√	√	√	No	8
Dubayova et al. 2010	√	√	√	√	√	√	√	√	√	√	√	Yes	11
*Falagas et al. 2007	√	x	√	x	x	x	x	x	√	x	√	No	4
Farooq et al. 2009	√	x	√	x	√	√	√	√	√	x	√	Yes	8
Hewitt et al. 2004	x	√	√	√	√	√	√	√	√	x	√	Yes	9

Study	1. A priori design	2. Duplicate study selection and extraction	3. Comprehensive literature review	4. Status of publication as inclusion criteria	5. List of studies (excluded and included)	6. Characteristics of studies	7. Scientific quality assessed	8. Scientific quality used in conclusions	9. Methods to combine findings appropriate	10. Publication bias assessed	11. Conflict of interest reported	3,6 and 7 apply	Overall score
Jones et al. 2010	√	√	√	√	x	√	x	√	√	√	√	No	9
Juarez Garcia et al. 2006	√	√	√	√	x	√	x	√	√	x	√	No	8
Khan and Amedia 2008	√	x	x	x	x	√	x	x	√	x	x	No	3
Koch et al. 2010	√	x	√	√	√	x	x	x	√	√	√	No	7
Koch and Iliffe 2011	√	x	√	√	√	√	√	√	√	√	√	Yes	10
*Kostopoulou et al. 2008	√	x	√	x	x	√	√	√	√	x	√	Yes	7
Kwan et al. 2004	√	x	√	x	x	√	√	√	√	x	√	Yes	7
Lecoutourier et al. 2010	√	√	√	x	√	√	√	√	√	x	√	Yes	9
Lecoutourier et al. 2010a	√	x	√	√	√	√	x	√	√	x	√	No	8
Liu et al. 2008	√	√	√	√	√	√	√	√	√	x	√	Yes	10
Lloyd Evans et al. 2011	√	x	√	√	√	√	√	√	√	x	√	Yes	9
*Main et al. 2010	√	√	√	√	√	√	√	√	√	x	√	Yes	10
Marshall et al. 2005	√	√	√	x	x	√	√	√	√	√	√	Yes	9
Marshall et al. 2011	√	√	√	√	√	√	√	√	√	√	√	Yes	11
Mitchell et al. 2011	√	x	√	x	√	√	√	x	√	x	√	Yes	7
Morrison et al. 2006	√	√	√	√	x	√	√	√	√	√	x	Yes	9
Navaneethan et al. 2008	√	√	√	√	√	√	x	√	√	√	√	No	10
Perkins et al. 2005	√	x	x	√	x	√	x	x	√	√	√	No	6
*Quirke et al. 2011	√	x	√	√	x	x	x	x	√	x	√	No	5
*Shojania et al. 2003	√	x	x	√	x	√	x	√	√	√	√	No	7
Smart et al. 2011	√	√	√	√	√	√	x	x	√	√	√	No	9
Sreeramareddy et al. 2009	√	√	√	√	√	√	√	x	√	√	√	Yes	10

Study	1. A priori design	2. Duplicate study selection and extraction	3. Comprehensive literature review	4. Status of publication as inclusion criteria	5. List of studies (excluded and included)	6. Characteristics of studies	7. Scientific quality assessed	8. Scientific quality used in conclusions	9. Methods to combine findings appropriate	10. Publication bias assessed	11. Conflict of interest reported	3,6 and 7 apply	Overall score
Storla et al. 2008	√	x	√	√	x	x	x	x	√	x	√	No	5
Usher Smith et al. 2011	√	√	√	√	√	√	√	√	√	√	√	Yes	11

* Studies marked with an asterix are systematic reviews for general reference only and not related to specific disease conditions

Table A4.2: Chronic Obstructive Pulmonary Disease: Quality Assessment of primary studies

Study	Sampling method	Independent variable reliably assessed	Dependent variable reliably assessed	Response rate	Adjustment for confounding	Statistical analysis	Overall grade of study	Relevance of study to review
Bastin et al. (2010	0	N/A	N/A	1	N/A	1	Medium	High
Bolton et al. (2004)	0	N/A	N/A	1	N/A	1	Medium	Medium
Calderon-Larranaga et al. (2010)	1	1	1	1	1	1	High	Medium
Frank et al. (2006)	0	N/A	N/A	1	N/A	1	Medium	High
Hassett et al. (2006)	0	N/A	N/A	1	N/A	1	Medium	Low
Jones et al. (2008)	0	N/A	N/A	1	N/A	1	Medium	High
Jordan et al. (2010)	1	1	1	1	N/A	1	High	High
Nacul et al. (2010)	1	1	1	1	1	1	High	High
Shahab et al. (2006)	1	1	1	1	N/A	1	High	High
Tinkelman et al. (2007)	0	N/A	N/A	0	N/A	1	Medium	High
Walker et al. (2006)	0	N/A	N/A	1	N/A	1	Medium	Medium

Table A4.3: Chronic Obstructive Pulmonary Disease: Quality Assessment for Outcome Evaluation

Study	Avoiding Selection Bias		Avoiding Attrition Bias			Avoiding Selective Reporting Bias		Was bias avoided?			Overall weight of evidence
	How were subjects allocated?	Adjustment for baseline imbalances in prognostic factors?	Attrition recorded separately for both groups?	Intervention group	Control group	Outcomes intending to measure?	For whom were outcomes given?	Selection	Attrition	Selective reporting	
Seamark et al. 2001	Non random	No	Yes	98%	33%	Health problem or state Time to complete assessment	All individuals and groups	No	No	Yes	Low

Table A4.4: Epilepsy: Quality Assessment of primary studies

Study	Sampling method	Independent variable reliably assessed	Dependent variable reliably assessed	Response rate	Adjustment for confounding	Statistical analysis	Overall grade of study	Relevance of study to review
Beach et al. (2005)	0	NA	NA	NA	NA	1	Medium	Low
Bhatt et al. (2005)	0	NA	NA	1	NA	1	Medium	Low
Brodie et al. (2007)	0	0	1	NA	NA	1	Medium	Low
O'Callaghan et al. (2011)	0	0	1	NA	1	1	Medium	Medium

Table A4.5: Tuberculosis: Quality Assessment of primary studies

Study	Sampling method	Independent variable reliably assessed	Dependent variable reliably assessed	Response rate	Adjustment for confounding	Statistical analysis	Overall grade of study	Relevance of study to review
Abubakar et al. (2008)	1	N/A	N/A	N/A	N/A	1	High	Medium
Craig et al. (2009)	0	N/A	N/A	1	N/A	1	Medium	High
Field et al. (2011)	0	N/A	N/A	1	N/A	1	Medium	Medium
French et al. (2009)	1	1	0	1	1	1	High	High
Jit et al. (2011)	0	N/A	N/A	N/A	N/A	1	Medium	High
Kothari et al. (2006)	0	N/A	N/A	N/A	N/A	1	Medium	High
Lewis et al. (2003)	0	N/A	N/A	1	N/A	1	Medium	High
Rodger et al. (2003)	0	1	0	1	1	1	Medium	High
White et al. (2002)	0	N/A	N/A	N/A	N/A	1	Medium	High

Table A4.6: Quality Assessment for Cluster Randomised Controlled Trial

Study	Avoiding Selection Bias		Avoiding Attrition Bias			Avoiding Selective Reporting Bias		Was bias avoided?			Overall weight of evidence
	How were units allocated?	Adjustment for baseline imbalances in prognostic factors?	Attrition recorded separately for both groups?	Intervention group	Control group	Outcomes intending to measure?	For whom were outcomes given?	Selection	Attrition	Selective reporting	
Griffiths et al. (2007)	Random	N/A	Yes	0%	0%	No cases of active and latent TB.	All individuals and groups	Yes	Yes	Yes	High

Table A4.7: Tuberculosis: Quality Assessment for Qualitative Studies

Study	Rigour in sampling	Rigour in data collection	Rigour in data analysis	Findings grounded in data	Breadth and depth of findings	Participants perspectives privileged	Reliability	Relevance
Metcalf et al. (2007)	Several steps taken	Several steps taken	Several steps taken	Well grounded	Good breadth, little depth	Somewhat	Medium	Medium
Nnoaham et al. (2006)	Several steps taken	Several steps taken	Several steps taken	Well grounded	Fair depth but little breadth	A lot	Medium	Medium

Appendix 5: Overlap of studies

Table A5.1: Primary studies common to systematic reviews examining late diagnosis for dementia.

	Systematic Reviews – Dementia		
	Bradford et al. (2009) n=40	**Koch et al. (2010) n=11**	**Koch and Iliffe (2011) n=5**
Primary Studies			
Adelman et al. 2004	x		
Allen et al. 2005		x	
Audit Commission 2000		x	
Boise et al. 1999a	x	x	
Boise et al. 1999b	x		
Bond et al. 2005	x		
Borson et al. 2006	x		
Brodaty et al. 1994	x		
Cahill et al. 2006	x		
Cahill et al. 2008		x	
Connell et al. 1996	x		
Downs et al. 2000	x		
Downs et al. 2006			x
Eefsting et al. 1996	x		
Glosser et al. 1985	x		
Hinton et al. 2004	x		
Hinton et al. 2007	x	x	
Illife et al. 2003	x		
Illife and Wilcock 2005	x	x	
Iliffe et al. 2006		x	
Incalzi et al. 1992	x		
Jones et al. 2006	x		
Kaduszkiewicz et al. 2008	x		
Knopman et al. 2000	X		
Lagaay et al. 1992	x		
Lopponen et al. 2003	x		
Milne et al. 2000	x		
Milne et al. 2005	x		
O'Connor et al. 1988	x		
Olafsdottir et al. 2000	x		
Olafsdottir et al. 2001	x	x	
Ortiz et al. 2000	x		
Perry et al. 2008			x
Renshaw et al. 2001	x		
Rimmer et al. 2005	x		
Ross et al. 1997	x		
Rondeau et al. 2008			x
Rubin et al. 1987	x		
Sternberg et al. 2000	x		
Teel et al. 2004	x	x	
Turner et al. 2004	x	x	
Valcour et al. 2000	x		
Van Hout et al. 2000	x	x	
Verhey et al. 1993	x		
Vernooji-Dassen et al. 2005	x		
Vollmar et al. 2010			x
Wakerbarth et al. 2002	x		
Waldorff et al. 2003			x
Wilkinson et al. 2005	x		

Table A5.2: Primary studies common to more than one systematic review examining late diagnosis for dementia.

	Courtwright and Turner (2010) n=19	Liu et al. (2008) n=5	Sreeramared dy et al. (2009) n=52	Storla et al. (2008) n=58
Primary studies				
Altet Gomez et al. 2003				x
Anastasatu et al. 1989				x
Asch et al. 1998				x
Ayuo et al. 2008			x	
Bai and Xiao 2004			x	x
Balasubramanian et al. 2004	x			
Bassili et al. 2008			x	
Caceres-Manrique and Orozco-Vargas 2008			x	
Cambanis et al. 2007				
Chavez 1998				x
Cheng et al. 1997		x		
Cheng et al. 2005			x	
Chang and Esterman 2007			x	
Chiang et al. 2005			x	x
Coreil et al. 2004	x			
Demissie et al. 2002			x	x
Deng et al. 2006			x	x
Dimitrova et al. 2006	x			
Enkhbat et al. 1997			x	x
Farah et al. 2006			x	x
Franco et al. 1996				x
Calder 2000				x
Gagliotti et al. 2006			x	x
Godfrey-Faussett et al. 2002	x			
Golub et al. 2006			x	x
Gulbaran et al. 1996				x
Guneylioglu et al. 2004			x	x
Hooi 1994			x	x
Karim et al. 2007			x	
Hudelson 1996	x			
Huong et al. 2007			x	
Jaramillo 1998	x			
Johansson et al. 1996	x			
Johannsson et al. 1999	x			
Johansson et al. 2000	x			
Kiwuwa et al. 2005	x		x	x
Lambert et al. 2005			x	
Lienhardt et al. 2001			x	x
Lawn et al. 1998			x	x
Liefooghe et al. 1997	x			
Lin et al. 2008			x	
Leung et al. 2007			x	
Lewis et al. 2003				x
Liam and Tang 1997			x	x
Long et al. 1999			x	x

	Courtwright and Turner (2010) **n=19**	**Liu et al. (2008)** **n=5**	**Sreeramareddy et al. (2009)** **n=52**	**Storla et al. (2008)** **n=58**
Lonnroth et al. 1999			x	
Maamari 2008	x		x	
Madebo and Lindtjorn 1999				x
Masjedi et al. 2002				x
Meintjes et al. 2008			x	
Mori et al. 1992			x	x
Needham et al. 2001				x
Ngamvithayapong et al. 2001			x	x
Niijima et al. 1990				x
Nkhoma et al. 1988				x
Noyes and Popay 2007	x			
Odusanya and Babfemi 2004			x	x
Okur et al. 2006			x	x
Ouedraogo et al. 2006				x
Paynter et al. 2004			x	
Pirkis et al. 1996				x
Pronyk et al. 2001			x	x
Pungrassami et al. 1993				x
Qureshi et al. 2008			x	
Rajeswari et al. 2002			x	x
Reznik and Ozuah 2006				
Roberts et al. 1983		x		
Rodger et al. 2003				x
Rojpibulstit et al. 2006			x	x
Rubel et al. 1992	x			
Sadiq and Muynck 2001				x
Sagbakken et al. 2008	x			
Salaniponi et al. 2000				x
Saly et al. 2006				x
Sasaki et al. 2000			x	x
Selvam et al. 2007			x	

	Courtwright and Turner (2010) n=19	Liu et al. (2008) n=5	Sreeramareddy et al. (2009) n=52	Storla et al. (2008) n=58
Sherman et al. 1999			x	x
Steen and Mazonde 1998			x	x
Tanke and Leirer 1994		x		
Tanke et al. 1997		x		
Tesena et al. 1991				x
Thorson and Johansson 2004	x			
Tobgay et al. 2006			x	
Wandwalo and Morkve 2000			x	x
Ward et al. 2001			x	x
Watkins and Plant 2004	x			
WHO 2004 (Egypt)				x
WHO 2004 (Iraq)				x
WHO 2004 (Yemen)				x
WHO 2006 (Iran)				x
WHO 2006 (Pakistan)				x
WHO 2006 (Somalia)				x
WHO 2006 (Syria)				x
Xu et al. 2005			x	x
Yamasaki et al. 2001			x	x
Yilmaz et al. 2001			x	
Yimer et al. 2005			x	x
Zerbini et al. 2008			x	

telephone: +44 (0)20 7947 9556   email: info@ioe.ac.uk