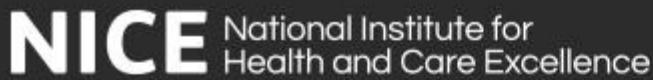


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Issue 76 – September 2015

This month in Eyes on Evidence

Mortality in people with attention deficit hyperactivity disorder

A Danish population cohort study reported that children, young people and adults with attention deficit hyperactivity disorder had a mortality rate double that of the general population, with accidents the most common cause of death.

Use of selective serotonin reuptake inhibitors or venlafaxine in early pregnancy

A Scandinavian cohort study found that taking specific selective serotonin reuptake inhibitors or venlafaxine in early pregnancy was associated with an increased risk of birth defects. However, the risk was not significant when infants exposed to these antidepressants were compared with brothers or sisters who had not been exposed.

Long-term outcomes after endovascular coiling for ruptured cerebral aneurysm

A cohort study of people in the UK with ruptured cerebral aneurysm reported that those who were treated with endovascular coiling were more likely to be alive and free of disability at 10 years than those who underwent neurosurgical clipping.

Silent cerebral infarctions in atrial fibrillation

A meta-analysis found that the risk of silent cerebral infarctions in people with atrial fibrillation was more than double that in people who did not have atrial fibrillation.

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Evidence summaries from NICE's Medicines and Prescribing Programme

NICE has recently published Medicines evidence commentaries on:

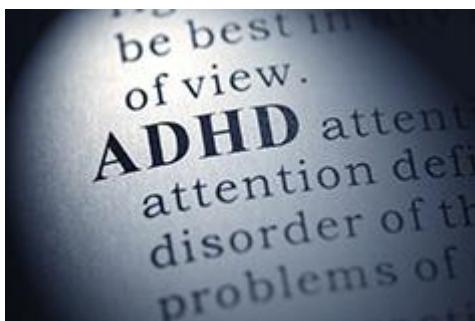
- Type 2 diabetes: implementing NICE guidance on self-monitoring of plasma glucose
- Digoxin in atrial fibrillation and congestive heart failure
- *Clostridium difficile*-associated diarrhoea: effects of PPIs and H₂ receptor antagonists on clinical response and recurrence

Case study from the Quality and Productivity collection

We highlight a new example from the Quality and Productivity collection showing how new local practices have both cut costs and improved quality:

- Home administration of intravenous diuretics to people with heart failure

Mortality in people with attention deficit hyperactivity disorder



Overview: Attention deficit hyperactivity disorder (ADHD) is a group of behavioural symptoms that includes inattention, hyperactivity and impulsiveness ([NHS Choices 2014](#)). Many people with ADHD will have coexisting conditions, such as disorders of mood, conduct and motor control ([NICE 2008](#)). People whose ADHD continues into adulthood often experience emotional and social difficulties, substance misuse, unemployment or involvement in crime.

Many severe mental and behavioural disorders appear to be associated with reduced life expectancy, both in terms of mortality from diseases and medical conditions and mortality from external causes ([Nordentoft et al. 2013](#)). Several of the factors associated with ADHD – such as substance misuse and comorbid mental disorders – may increase mortality in people with the condition.

Current advice: The NICE guideline on [attention deficit hyperactivity disorder \(currently being updated\)](#) recommends that children and young people with ADHD should be treated with individual or group behavioural or psychological treatment (cognitive behavioural therapy, social skills training or both). Children and young people may also be treated with medicines, or both medicines and behavioural or psychological treatments, depending on the severity of ADHD and impairment. Medicines are the first-line treatment for adults with ADHD.

Before starting pharmacological treatment for ADHD, children, young people and adults should undergo a full assessment. This assessment should include a full mental health and social assessment and a risk assessment for substance misuse and drug diversion (where a medicine is passed on to others for non-prescription use). Treatment plans should be developed for any coexisting conditions.

The NICE pathway on [attention deficit hyperactivity disorder](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: [Dalsgaard et al. \(2015\)](#) used a national Danish cohort to assess the risk of mortality in people with ADHD compared with people in the general population. People born between 1981 and 2011 were identified from the Danish Civil Registration System and followed up from 1995 or their first birthday (whichever came last) to 2013. Linked data on diagnosis of ADHD and other comorbid mental disorders,

and on date and cause of death, were obtained from other national registers.

The study cohort comprised 1,922,248 people followed up for up to 32 years (24,907,560 person-years). A total of 32,061 people in the cohort had a diagnosis of ADHD (183,049 person-years of observation), 107 of whom died during follow-up. All-cause mortality was 5.85 per 10,000 person-years among people with ADHD, compared with 2.21 per 10,000 person-years in people without ADHD. The risk of death among people with ADHD was more than double that in the general population (adjusted mortality rate ratio [MRR]=2.07, 95% confidence interval [CI] 1.70 to 2.50, $p<0.0001$).

Age at diagnosis of ADHD was associated with mortality, with the risk of death highest among people diagnosed in adulthood (adjusted MRR=4.25, 95% CI 3.03 to 5.78). Mortality among people with ADHD was also affected by comorbid oppositional defiant disorder or conduct disorder (adjusted MRR=2.17, 95% CI 1.33 to 3.31) and by coexisting substance misuse (adjusted MMR=5.63, 95% CI 3.69 to 8.16). Among people without these comorbid conditions, mortality was higher in girls and women with ADHD (adjusted MRR=2.85, 95% CI 1.56 to 4.71) than in boys and men (MRR=1.27, 95% CI 0.89 to 1.76).

Data on cause of death were available for 79 of the 107 people with ADHD who died: 54 (68.4%) died from unnatural causes (42 [77.8%] of these deaths were accidents) and 25 (31.6%) died from natural causes. Deaths from unnatural causes were more than 2 times higher in people with ADHD than in the general population (adjusted MRR=2.40, 95% CI 1.81 to 3.13, p value not reported), and deaths from natural causes were 70% higher (adjusted MRR=1.70, 95% CI 1.11 to 2.47, $p=0.016$).

Limitations of this analysis include that the national registers did not encompass people diagnosed in private practice, so the results may not apply to all people with ADHD. In addition, the authors could not control for all comorbid psychiatric disorders that may affect people with ADHD, and those that the analysis did account for may be underdiagnosed.

Commentary by Professor Eric Taylor, Emeritus Professor of Child and Adolescent Psychiatry, King's College London:

"Before this paper was published, we knew that ADHD is often impairing in adult life; now, we see that it can be lethal. The existing NICE guidance makes it plain that health services should be able and willing to manage continuing impairment in people who continue to have ADHD in adulthood. This study adds force to the argument.

"The key finding, that mortality is increased in adults with ADHD, is very likely to be robust. It is based on a large population sample, using the excellent documentation of health status available in Denmark. The researchers were able to account for a good selection of potentially confounding influences that might have led to misleading results.

"The study was also able to ask about the factors that made death more likely. Oppositional and conduct disorders, and the associated problem of substance misuse, increased the risk considerably. Indeed, their influence could even be greater than suggested by this study. All these factors could still be risky even if they are present at a lower level than would lead to an actual clinical diagnosis. These factors are all possible complications of ADHD, so the implication is that clinics treating people with ADHD should recognise their importance – preferably before they become dangerous. Systematic screening in clinics would be advisable, and preventive education is also feasible.

"Even if these complications did not develop, ADHD was still a risk factor for mortality. This could well be because the core problem of impulsiveness is a cause of accidents, and accidents were the major cause of death. The implication is that a reduction in impulsiveness (if necessary, with medication) should be a target for long-term management. This is implicit in existing guidance, but is now spelled out forcefully by this study.

"Two other influences linked to death in ADHD emerged from the study: a late diagnosis and female gender. Girls and women with ADHD are less likely to be diagnosed. These two factors could both be testimony to the hazards of failing to make a timely diagnosis and provide prompt intervention. The study should be significant in emphasising the important effects of ADHD in adulthood and the need for

treatment.”

Study sponsorship: Lundbeck Foundation.

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Use of selective serotonin reuptake inhibitors or venlafaxine in early pregnancy

Overview: Deciding whether to use medication to treat mental health problems in women who are pregnant can be difficult. If a woman with a severe mental health problem stops taking her medication when she becomes pregnant, she may adversely affect her own mental health and her ability to care for her unborn child ([Kalifeh et al. 2015](#)). However, as with most evidence generated in this field, there are no randomised controlled trials on the efficacy of antidepressants in pregnancy, and safety data for this group come from observational studies.



Studies of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants during pregnancy, are conflicting. The most consistent birth defects reported are cardiovascular defects, while other birth defects – such as anal and urethral defects, clubfoot and abnormally shaped skull – have also been reported in early pregnancy, but less consistently. Taking the noradrenaline reuptake inhibitor [(S)NRI] venlafaxine in early pregnancy has been associated with several types of birth defect ([Polen et al. 2013](#)).

Current advice: The NICE guideline on [antenatal and postnatal mental health](#) gives specific advice on managing depression in women during pregnancy and the postnatal period. Non-pharmacological treatments are recommended for persistent subthreshold depressive symptoms, or mild to moderate depression, unless there is a history of severe depression. The following options may be considered for women who currently have moderate or severe depression:

- a high-intensity psychological intervention (for example, cognitive behavioural therapy)
- a tricyclic antidepressant, SSRI or (S)NRI if she understands the risks associated with the medication and the mental health problem in pregnancy and the postnatal period and:
 - she has expressed a preference for medication or
 - she declines psychological interventions or
 - her symptoms have not responded to psychological interventions
- a high-intensity psychological intervention in combination with medication if she understands the risks associated with the medication and the mental health problem in pregnancy and the postnatal period, and there is no response, or a limited response, to a high-intensity psychological intervention or medication alone.

[MHRA guidance on SSRIs and \(S\)NRIs](#) highlights a small increase in the risk of cardiovascular defects from about 1 in 1000 to less than 2 in 1000 when paroxetine and fluoxetine are taken during the first trimester. It also discusses risks for the newborn when antidepressants are taken later in pregnancy. The [UK Teratology Information Service](#) provides advice to NHS professionals on medicine use in pregnancy.

The NICE pathway on [antenatal and postnatal mental health](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A population-based cohort study ([Furu et al. 2015](#)) looked at whether taking specific SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram) or venlafaxine in early pregnancy was associated with an increased risk of birth defects, particularly cardiovascular defects.

National health registers for Denmark, Finland, Iceland, Norway and Sweden were used to identify 2.3 million women who had single births between 1996 and 2010. Filled prescriptions for an SSRI or venlafaxine from 30 days before the first day of the last menstrual period until the end of the first trimester were considered, and outcomes of the infant up to a year after birth were studied.

Diagnosis of major birth defects was 13% higher among the 36,772 infants exposed to SSRIs or venlafaxine during the first trimester than in the 2,266,875 unexposed infants (adjusted odds ratio [OR]=1.13, 95% confidence interval [CI] 1.06 to 1.20; absolute risk=3.7% versus 3.2%).

Infants exposed to SSRIs or venlafaxine had a 15% relative increase in cardiac birth defects overall (adjusted OR=1.15, 95% CI 1.05 to 1.26; absolute risk=1.5% versus 1.2%). When specific cardiac defects were considered, infants exposed to SSRIs or venlafaxine had a higher level of right ventricular outflow tract obstruction defects (adjusted OR=1.48, 95% CI 1.15 to 1.89) and atrial and ventricular septal defects (OR=1.17, 95% CI 1.05 to 1.31).

Fluoxetine, paroxetine and citalopram were all associated with cardiac defects, whereas a significant effect was not reported with other specific SSRIs and venlafaxine. Clubfoot, abdominal wall defects (omphalocele) and anal defects were also reported.

The authors then did a sibling analysis that compared 980 infants who had been exposed to SSRIs or venlafaxine with 1308 brothers or sisters who had not been exposed. The associations between SSRIs or venlafaxine and birth defects were no longer statistically significant in this analysis (major birth defects adjusted OR=1.06, 95% CI 0.91 to 1.24; cardiac birth defects adjusted OR=0.92, 95% CI 0.72 to 1.12; right ventricular outflow tract obstruction defects adjusted OR=0.56, 95% CI 0.21 to 1.49).

A strength of this study is the large number of women in the cohort. Limitations include the smaller numbers in the sibling analysis and, therefore, lower statistical power. In addition, non-adherence to dispensed antidepressants may have caused misclassification of exposure, and the analysis did not adjust for all confounding factors, such as lifestyle, alcohol consumption and depression severity.

Commentary by Louise Jackson, Chief Pharmacist, North Staffordshire Combined Healthcare NHS Trust:

“The initial analyses in this study found an increased risk of any birth defect and overall cardiac birth defects in women exposed to SSRIs or venlafaxine in pregnancy. In particular, the prevalence of septal defects and right ventricular outflow tract defects was higher in exposed infants. However, Furu et al. (2015) concluded that exposure to these medicines during pregnancy was not associated with a ‘substantial’ increase in birth defects, with the lack of an association in the sibling controlled analyses pointing against a teratogenic effect of SSRIs or venlafaxine.

“This population-based cohort study is extensive including 2.3 million infants, of which 1.6% were assumed to have exposure to SSRIs or venlafaxine during the first trimester. However, fewer than 1000 exposed infants were assessed in the sibling comparison. This small number of cases made it difficult to detect statistically significant differences given that these birth defects are known to occur in around 1 per 1000 live births in non-exposed infants.

“An additional study by [Reefhuis et al. \(2015\)](#) found that only paroxetine and fluoxetine were associated with birth defects, similar to Furu et al. (2015). The strongest effect sizes seemed to be for paroxetine on neural tube and abdominal wall defects (anencephaly and omphalocele). The effects of paroxetine and fluoxetine on cardiac defects were a little greater than those reported by Furu et al. (2015). As in the Furu study, despite the large number of live births reviewed, only small numbers of infants exposed to SSRIs were included in fully adjusted analyses (n=957).

“Both studies provide further evidence to inform discussions with women considering taking SSRIs during pregnancy. However, these studies focused on live births, so do not have any information on whether SSRIs affected stillbirth or defects identified in pregnancy, and had low numbers of infants exposed to individual medicines. The results do not lead to any new conclusions, and add to the previous studies that have shown inconsistent results.

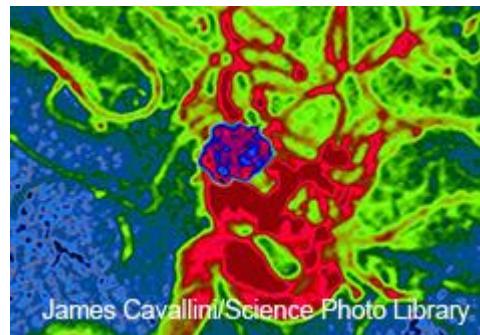
“Overall, the results from Furu et al. (2015) support current NICE recommendations. In particular, these findings emphasise the importance of reviewing each case individually to ensure optimum treatment. Where use of an antidepressant is considered appropriate, women should be made aware of both the risk of harm from medication and the risk of ineffective treatment – and this new evidence helps to clarify that.”

Study sponsorship: Apoteksbolaget.

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Long-term outcomes after endovascular coiling for ruptured cerebral aneurysm



Overview: A cerebral aneurysm is a bulge in a blood vessel in the brain caused by weakness in the wall of the vessel ([NHS Choices 2013](#)). Cerebral aneurysms can burst and cause bleeding on the surface of the brain – known as subarachnoid haemorrhage. Outcomes are poor for people with subarachnoid haemorrhage from rupture of a cerebral aneurysm: half die within 1 month of the haemorrhage ([National Confidential Enquiry into Patient Outcome and Death 2013](#)).

Ruptured cerebral aneurysm can be treated either surgically or with endovascular coiling ([NHS Choices 2013](#)). Neurosurgical clipping involves opening the skull

and sealing the neck of the aneurysm with a metal clip. Endovascular coiling comprises inserting a coil into the aneurysm, which causes clotting and stops blood from entering ([NICE 2005](#)). The coil is placed using a thin tube that is inserted into a large artery, usually in the groin, and passed up into the skull.

The [International Subarachnoid Aneurysm Trial \(ISAT\)](#) was a multicentre randomised controlled trial in Europe and North America. The study investigated endovascular coiling compared with neurosurgical clipping in people with ruptured cerebral aneurysm. The results showed that endovascular coiling was associated with better survival free of disability at 1 year than neurosurgical clipping ([Molyneux et al. 2002](#)). However, recurrence of aneurysm rupture (rebleeding) at 1 year and at up to 7 years was higher in people who underwent endovascular coiling ([Molyneux et al. 2005](#)).

Current advice: NICE interventional procedure guidance on [coil embolisation of ruptured intracranial aneurysms](#) supports use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.

Endovascular coiling should only be performed in specialist units with expertise in the endovascular treatment of cerebral aneurysm. Clear arrangements should be in place for the involvement of different clinical disciplines in treatment and follow-up.

The NICE pathway on [neurological conditions](#) brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

New evidence: [Molyneux et al. \(2015\)](#) assessed long-term follow-up data from UK participants in ISAT. ISAT randomly assigned people with ruptured cerebral aneurysm to endovascular coiling (n=1073) or neurosurgical clipping (n=1070). All participants completed a questionnaire each year on their dependency and disability status and on whether they had experienced recurrent rupture of a cerebral aneurysm.

This analysis considered the 1644 patients enrolled at the 22 UK centres in ISAT (n=809 in the endovascular coiling group and n=835 in the neurosurgical clipping group). People treated with endovascular coiling were more likely to be alive at 10 years than those treated with neurosurgical clipping (83% versus 79%; odds ratio [OR]=1.35, 95% confidence interval [CI] 1.06 to 1.73).

A total of 1003 (75%) of the 1331 people who were still alive 10 years after they were enrolled had returned a questionnaire (n=531 in the endovascular coiling group and n=472 in the neurosurgical clipping group). These questionnaire results showed that the 2 groups did not differ in the proportion of participants who were independent and free from significant disability at 10 years (82% versus 78%; OR=1.25; 95% CI 0.92 to 1.71). However, the probability of being alive and independent at 10 years was higher in the endovascular coiling group than in the neurosurgical clipping group (probability=0.682, OR=1.34, 95% CI 1.07 to 1.67).

Overall, 33 patients had further cerebral aneurysm rupture between 1 and 17 years after their initial haemorrhage: 21 people in the endovascular coiling group and 12 people in the neurosurgical clipping group. More patients in the endovascular coiling group (n=13) than the neurosurgical clipping group (n=4) experienced recurrence and rupture of the aneurysm targeted by the intervention (rebleed). The risk of death or disability from this recurrent aneurysm rupture was 1 in 1397 patient-years in the endovascular coiling group and 1 in 2041 patient-years for the neurosurgical clipping group.

Limitations of this study include that the results apply only to people with ruptured cerebral aneurysm who are suitable for both endovascular coiling and neurosurgical clipping. In addition, angiograms were not performed during long-term follow-up to determine the risk of recurrent rupture.

Commentary by Nitin Mukerji, Consultant Neurosurgeon with a specialist interest in neurovascular surgery, James Cook University Hospital, Middlesbrough:

“The results from this 10-year follow-up study show the safety and efficacy of endovascular coiling as a valid alternative to neurosurgical clipping in selected patients. At 10 years, more patients treated with endovascular coiling were alive than patients who underwent neurosurgical clipping. However, among the patients who completed the questionnaire at 10 years, no significant differences were seen between the 2 groups in the numbers reporting good independence and disability outcomes. The derivation and methodology behind the significantly higher odds of independent survival at 10 years in the endovascular coiling group are debatable and have been subject to criticism (for example, [Thomas and Ogilvy 2014](#)).

“Meta-analyses of studies evaluating coil embolisation have revealed a recanalisation rate of 20% after this procedure ([Rezek et al. 2013](#)). The ISAT group had earlier reported a significantly higher rate of aneurysm recurrence and rupture in the endovascular coiling group in the first year ([Molyneux et al. 2002](#)). This paper reports such rebleed events after the first year, and the rebleed rates in the endovascular group continue to be higher. The absolute rates of rebleeding are low, but in this day and age is even 1 rebleed acceptable?

“The lack of radiological and angiogram follow-up is a serious drawback of this study. The authors question the value of radiological surveillance. But this must be the subject of further study, because there is insufficient evidence to give up radiological surveillance altogether. The correlation of radiological recanalisation with rebleeding needs to be accurately determined to minimise the cost of radiological surveillance and repeated coiling procedures.

“It is likely that the ISAT data are now outdated and that endovascular technology and experience has moved on significantly. Real-world results of this procedure are likely to be even better than those from ISAT.

“A reasonable and balanced conclusion from this study would be that endovascular coiling for good grade, ruptured aneurysms results in similar 10-year outcomes to neurosurgical clipping but perhaps a higher rate of rebleeding. Endovascular coiling should be considered as a first-line treatment for ruptured aneurysms. It has good long-term outcome and is durable.

“However, the results of ISAT should not be blindly applied to every aneurysm, especially unruptured aneurysms. There is no substitute for treatment on a case-by-case basis, with multidisciplinary discussion between the surgical and radiological teams.”

Study sponsorship: UK Medical Research Council.

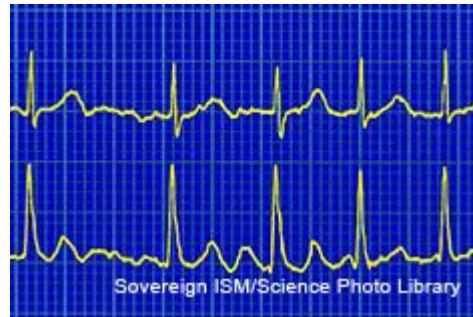
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Silent cerebral infarctions in atrial fibrillation

Overview: Atrial fibrillation is a heart condition that causes an irregular and often abnormally fast heart rate. People with atrial fibrillation are at increased risk of stroke ([Wolf et al. 1991](#)). People with atrial fibrillation are also at increased risk of cognitive impairment, even if they have not had a symptomatic stroke ([Kalantarian et al. 2013](#)). A possible mechanism for this association is that people with atrial fibrillation may be more likely to experience silent cerebral infarctions ([Das et al. 2008](#)).

A silent cerebral infarction is a brain lesion caused by a vascular occlusion, which is often found incidentally by MRI or CT in otherwise healthy people or during autopsy ([Lee et al. 2000](#)). The prevalence of MRI-diagnosed silent cerebral infarctions in healthy elderly people is 20% ([Vermeer et al. 2007](#)). Silent cerebral infarctions may be precursors of symptomatic stroke and cause progressive brain damage that may be associated with vascular dementia.



Current advice: The NICE clinical guideline on [atrial fibrillation](#) recommends using the [CHA₂DS₂-VASc stroke risk score](#) to assess the risk of stroke in people with atrial fibrillation who have any of the following characteristics:

- symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

The CHA₂DS₂-VASc score uses a number of risk factors – including history of stroke, transient ischaemic attack or thromboembolism – to estimate the risk of stroke in people with atrial fibrillation. Anticoagulation treatment with [apixaban](#), [dabigatran etexilate](#), [rivaroxaban](#) or a vitamin K antagonist should be considered in men with a CHA₂DS₂-VASc score of 1 and men or women with a CHA₂DS₂-VASc score of 2 or above.

The NICE pathway on [atrial fibrillation](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A meta-analysis by [Kalantarian et al. \(2014\)](#) investigated the risk of silent cerebral infarctions in people with atrial fibrillation who had not experienced a stroke.

The authors identified observational studies of the association between atrial fibrillation and silent cerebral infarctions in people who had no history of acute or symptomatic stroke. Silent cerebral infarctions were defined as evidence of brain infarctions on imaging or autopsy with no attributable clinical symptoms (such as neurological deficits).

A total of 17 studies (n=7773) from 7 countries were identified, 3 of which were prospective. Silent cerebral infarctions were identified by CT in 6 studies, MRI in 9 studies, and autopsy in 2 studies. The pooled prevalence of silent cerebral infarctions in people with atrial fibrillation was 40% (95% confidence interval [CI] 29% to 51%) in those who underwent MRI and 22% (95% CI 13% to 32%) in those who had CT.

Analysis of the association between atrial fibrillation and silent cerebral infarctions was restricted to 9 studies (n=4407) that used imaging for diagnosis and reported risk estimates. Overall, 230 (46%) people with atrial fibrillation and 610 (16%) people without atrial fibrillation had silent cerebral infarctions. The risk of silent cerebral infarctions was twice as high in people with atrial fibrillation compared with those who did not have atrial fibrillation among people with no history of symptomatic stroke (odds ratio=2.62, 95% CI 1.81 to 3.80).

Limitations of this analysis included that many of the studies were retrospective and cross-sectional, and the studies were of variable quality. Autopsy studies were heterogeneous and low quality, so were excluded from the meta-analysis. Information on the anticoagulation status of participants was not available for many studies, and the prevalence of silent cerebral infarctions diagnosed by MRI varied depending on the diagnostic criteria used.

Commentary by Professor Jonathan Mant, Professor of Primary Care Research, Primary Care Unit, University of Cambridge:

“This study adds to the body of research that suggests that atrial fibrillation is associated with increased risk of cognitive impairment and dementia, by providing evidence of the likely mechanism through which it might do this – that is, by increasing risk of silent cerebral infarction.

“A mainstay of treatment of atrial fibrillation is to reduce risk of stroke through anticoagulation. Currently, anticoagulation is offered on the basis of an assessment of the risk of clinical stroke in atrial fibrillation using the CHA₂DS₂-VASc score. This study raises the question as to whether risk of silent cerebral infarction also needs to be taken into account in decisions concerning anticoagulation.

“However, there are two questions that need to be answered before any changes to current practice are considered. Firstly, does anticoagulation reduce risk of silent cerebral infarction, and risk of cognitive impairment and dementia? If this was the case, the risk:benefit ratio and indeed the cost effectiveness of anticoagulation could change, so that anticoagulation might become indicated for people with atrial fibrillation who are at lower risk of stroke. Secondly, does presence of silent cerebral infarction increase risk of subsequent clinical stroke? If this was the case, then some refinement of the CHA₂DS₂-VASc score might be necessary.

“Unfortunately, there are no randomised trials or clear-cut evidence from observational studies to answer either of these questions. Pending such research, this meta-analysis raises our awareness of the potential invisible impact of atrial fibrillation over and above the recognised overt clinical manifestations.”

Study sponsorship: Deane Institute for Integrative Research in Atrial Fibrillation and Stroke, Massachusetts General Hospital.

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Neighbourhood fast-food outlets and type 2 diabetes



Overview: Diabetes mellitus is a group of metabolic disorders in which blood glucose is persistently raised ([NICE 2015](#)). People with type 1 diabetes are deficient in insulin, the hormone responsible for promoting glucose absorption, whereas those with type 2 diabetes are resistant to insulin and may not release sufficient insulin from their pancreas.

In England in 2010–12, 12.4% of people aged 18 years and over who were obese had diagnosed diabetes, 5 times the proportion among people with a healthy weight ([Public Health England 2014](#)). Exposure to fast-food

outlets has been shown to increase BMI and the risk of obesity ([Burgoin et al. 2014](#)), and could therefore also increase the risk of type 2 diabetes.

Current advice: The NICE guideline on [preventing type 2 diabetes: population and community-level interventions](#) recommends that people should consume as little as possible of: fried food; drinks and confectionery high in added sugars (such as cakes, pastries and sugar-sweetened drinks); and other food high in fat and sugar (such as some take-away and fast foods).

Commissioners and local authorities should work with local food retailers, caterers and workplaces to encourage local provision of affordable fruit and vegetables and other food and drinks that can contribute to a healthy, balanced diet. Existing planning mechanisms should be used to increase the opportunities available for local people to adopt a healthy diet. For example, planning policies should consider healthier eating when reviewing applications for new food outlets.

The NICE pathway on [preventing type 2 diabetes](#) brings together all related NICE guidance and associated products on the area in a set of interactive topic-based diagrams.

New evidence: [Bodicoat et al. \(2014\)](#) analysed cross-sectional data from 3 UK studies to investigate whether the number of fast-food outlets in a neighbourhood was associated with type 2 diabetes in the residents.

Data were taken from 2 randomised controlled trials that recruited people at high risk of developing diabetes ([Let's Prevent Diabetes](#) and [Walking Away from Diabetes](#)) and 1 trial that recruited people in the general population ([ADDITION-Leicester](#)). These studies recruited people from primary care (response rate=22%) and screened them for type 2 diabetes. Participants were then randomly assigned to a healthy lifestyle intervention or a cardiovascular risk management programme. Bodicoat et al. (2014) used the cross-sectional data from the screening stage of each study.

The absolute number of fast-food outlets in the participants' neighbourhoods was measured using listings in an online business directory. Businesses advertising 'fast food', 'fish and chips' or 'take away' were categorised as fast-food outlets. 'Neighbourhood' was defined as within 500m of a participant's home, as determined by their postcode.

A total of 10,461 people aged 59 years on average were included in this study. More than half (53%) of participants were male and 21% were from black, Asian and minority ethnic groups. On average, participants had 2.1 fast-food outlets in their neighbourhood.

Analyses of the link between fast-food outlets and type 2 diabetes were adjusted for social deprivation, rural or urban location, ethnicity, age and sex. The number of fast-food outlets in a neighbourhood was associated with a slightly higher risk of type 2 diabetes (odds ratio [OR]=1.02, 95% confidence interval [CI] 1.00 to 1.04, $p=0.02$). This finding corresponds with 1 extra case of type 2 diabetes for every 2 additional

outlets per 200 residents or in a 500m radius.

The number of fast-food outlets also had small associations with obesity (OR=1.02, 95% CI 1.01 to 1.03, p<0.01) and BMI (unstandardised regression coefficient=0.04, 95% CI 0.00 to 0.08, p<0.01).

The authors warn that the cross-sectional nature of the study means that it is not possible to infer a causal effect of fast-food outlets on diabetes and obesity. In addition, the number of fast-food outlets was measured in 2014, but participants were screened for diabetes up to 10 years earlier (2004–11). Two of the trials that provided data for this analysis specifically recruited people at high risk of type 2 diabetes.

Commentary by Esther Trenchard-Mabere, Associate Director of Public Health, London Borough of Tower Hamlets:

“This study builds on existing evidence of an association between the number of fast-food outlets in a neighbourhood and the prevalence of adult obesity. It adds to this evidence by also showing a small but statistically significant association with the prevalence of screen-detected type 2 diabetes.

“A strength of this study is that it demonstrates that these associations, although reduced, remain statistically significant after adjusting for possible confounders. This finding could strengthen the case for restricting or reducing the numbers of fast food outlets in an area on public health grounds when considering planning permission.

“However, as the authors acknowledge, the study is not able to demonstrate that the association between fast-food outlets and diabetes and obesity was causal. The biggest weakness is that the estimation of the number of fast-food outlets was collected several years after the health outcomes data. This issue of timing is particularly pertinent. As the authors point out, it is possible that demand precedes increased supply, with the high number of fast-food outlets reflecting the preferences of local residents.

“However, this might not be a simple question of which is the cause and which is the effect. Another possibility is that exposure to fast-food outlets could lead to the formation of habits, increasing demand and further stimulating supply in a classic positive feedback loop. Different answers to the question of cause and effect (individual preferences versus availability or exposure) could be obtained depending on the methodology and type of data collected. A methodology based on systems thinking that maps the complex inter-relationships and identifies feedback loops might be more appropriate than a linear model that attempts to control for confounders.

“Strengthening the evidence on the impact of fast food availability on health outcomes is important. But many of the difficulties in implementing restrictions to the number of fast-food outlets are related to wider economic and social considerations – for example, the impact on the local economy – that require different types of evidence to address.”

Study sponsorship: National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands, the Leicester Clinical Trials Unit, and the NIHR Leicester – Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit.

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Evidence summaries from NICE's Medicines and Prescribing Programme

NICE has recently published the following Medicines evidence commentaries:

[Type 2 diabetes: implementing NICE guidance on self-monitoring of plasma glucose](#)

An observational study involving 139 GP practices in the UK assessed the effect of local interventions on the inappropriate implementation of NICE guidance on the self-monitoring of blood glucose in people for whom it is unlikely to be beneficial.

Digoxin in atrial fibrillation and congestive heart failure

A meta-analysis of 19 studies investigated whether digoxin affected all-cause mortality in people with atrial fibrillation or congestive heart failure.

Clostridium difficile-associated diarrhoea: effects of PPIs and H₂ receptor antagonists on clinical response and recurrence

A post-hoc observational analysis of data from 2 randomised controlled trials assessed whether proton pump inhibitors or H₂ receptor antagonists affected clinical response to fidaxomicin or vancomycin in patients with diarrhoea associated with *Clostridium difficile* infection.

Medicines evidence commentaries form part of NICE's [Medicines Awareness Service](#) and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. These commentaries were published in NICE's [Medicines Awareness Weekly](#) service and are available online in [NICE Evidence Search](#).

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Case study from the Quality and Productivity collection

Heart failure is a debilitating condition that affects the day-to-day lives of many people in the UK. The disorder is characterised by fatigue, breathlessness and retention of fluid. Diuretic tablets help reduce fluid retention, but are often not enough to control symptoms as the disease progresses. Subsequently people usually need to be admitted to hospital to be treated with intravenous (IV) diuretics.

UK health policy is shifting towards care being provided as close to home as possible. This is driven by the twin priorities of improving quality and increasing cost effectiveness.

The British Heart Foundation set up a 2-year pilot programme to assess safe and effective ways for specialist nursing teams to administer IV diuretics to people at home or in a day care setting. The aims of the pilot were to prevent hospital admissions and improve patient experience.

The pilot was delivered at 10 NHS sites across the UK. Heart failure specialist nurses developed and delivered community-based IV diuretic services as part of existing heart failure services.

At each site, a lead nurse set up a consultation process with people who had heart failure to identify the need for the service. People who did not respond to oral diuretics were offered IV diuretics in their home or in community day care settings such as a hospice or community hospital.

Although the pilot projects were set up as stand-alone home-based IV diuretic services, they developed into integrated parts of wider heart failure care packages.

The latest data show that 79% of IV diuretic interventions did not involve hospital admission, preventing 869 hospital bed days over the duration of the pilot. A total of 63% of IV interventions were successful, resulting in oedema reduction, weight loss and symptom resolution. The cost of delivering home-based IV diuretics was 77% less than the cost of hospital admission for heart failure.

The pilot met its deliverables across clinical effectiveness, safety, patient and carer experience, and cost effectiveness, indicating that this approach is an effective way of delivering home-based IV diuretics.

Simon Gillespie, Chief Executive of the British Heart Foundation, said: "This programme saw a significant improvement in patient and carer experiences. All the 55 patients surveyed found the treatment preferable to hospital admission and said that if they needed IV diuretics again, they would choose to have them at home rather than in hospital. The main reasons were being able to stay with loved ones; the convenience, privacy and minimal disruption to day-to-day life; having the time to do what they wanted; and being comfortable and relaxed rather than stressed."

"An additional outcome was that there was more time for patient and carer education on the treatment and addressing wider care needs of people in the community. An example from 1 site is where treatment of a patient in their home led to the provision of social care, home adaptations and a pendant alarm service. This would not have happened in a hospital setting without the British Heart Foundation programme in place.

"British Heart Foundation is proud to have funded and supported a high quality programme that bridged a gap in services that people want and need. The programme has been successful and had such positive outcomes that plans are underway in several areas to adopt the model as part of service redesign."

The overall cost saving for the service was £162,740 across the 10 sites. However, if the services run at full capacity, then this saving is forecasted to be much higher. Further cost savings are expected through a reduction in consultant time compared with time supporting the service within the hospital and a reduction in ambulance costs for admissions.

A full breakdown of costs to achieve these savings can be found within the [2014 evaluation report](#).

The NICE Quality and Productivity collection provides users with practical case studies that address the quality and productivity challenge in health and social care. All examples submitted are evaluated by NICE to assess the degree to which the initiative meets the Quality and Productivity criteria: savings, quality, evidence and implementability.

Visit the [NICE website](#) for more details of [home administration of intravenous diuretics to heart failure patients](#) and [other examples](#) of quality and productivity initiatives.

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