Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction
Dr Jez Thompson
GP Leeds and Clinical Director Lifeline (North) RCGP regional lead substance misuse

Cardiovascular disease
Dr Peter Savill
GP Watercress Medical, Medstead
GPwSI Cardiology, Southampton

Diabetes
Dr Matthew Lockyer
GP Suffolk and hospital practitioner in diabetic medicine

Dr Peter Savill
GP Watercress Medical, Medstead
GPwSI Cardiology, Southampton

Mental health
Dr Phillip Bland
GP with an interest in mental health, Dalton-in-Furness

Obstetrics and gynaecology
Dr Chris Barclay
GP with an interest in O&G, Suffolk

Paediatrics
Dr Chris Barclay
GP with an interest in O&G, Suffolk

Sexual health
Dr Richard Ma
GP with an interest in sexual health
NIHR Research Fellow, Imperial College, London

Smoking cessation
Dr Jez Thompson
GP Leeds and Clinical Director Lifeline (North) RCGP regional lead substance misuse

Urology
Dr Jonathan Rees
GPwSI Urology, Bristol

Diabetes

Consumption of sugar sweetened drinks linked to type 2 diabetes

A large meta-analysis, recently published in the *BMJ*, has shown that drinking sugar sweetened beverages raises the risk of type 2 diabetes, independent of obesity.

PubMed, Embase, Ovid and Web of Knowledge were searched for eligible papers. Studies were graded for quality and discussed using a standard protocol.

From a total of 1,937 articles, 33 were reviewed in full text and 21 articles, following 16 cohorts of patients, were included in the analysis. Unpublished but eligible data on a further cohort were added giving an overall total of 17 cohorts. The analysis covered 38,253 cases of type 2 diabetes over 10,126,754 person-years in total. None of the studies analysed was funded by industry.

Information was gathered about the intake of sugar sweetened drinks, artificially sweetened drinks and fruit juices. The data were standardised to measure the association of one serving of 250 ml per day on the risk of incident diabetes.

For sugar sweetened drinks, one 250 ml drink per day was associated with an 18% greater incidence of type 2 diabetes (95% CI: 8.8-28%). When adjusted for obesity the risk was attenuated to a 13% increase (95% CI: 5.8-21%), see table 1, below.

Artificially sweetened drinks were also associated with a greatly increased incidence of diabetes; 25% (95% CI: 18-33%), but this was attenuated to 8% after adjustment for obesity (95% CI: 2.1-15%).

Fruit juice intake was also associated with a raised risk of incident diabetes, 5% (95% CI: -1 to 11%) and this was increased after adjustment for obesity, to 7% (95% CI: 0.8-14%).

Further statistical analysis for confounding factors suggested that the sugar sweetened drink risk was likely to be a true finding, but the increased risk from artificially sweetened drinks and fruit juices was likely to be exaggerated by publication bias and confounding variables.

Assuming a causal relationship between increased intake of sugar sweetened drinks and type 2 diabetes, the authors estimated the increased population risk for the UK and the USA. Over a decade, they predicted 79,000 extra cases in the UK and 1.8 million in the USA. A large proportion of the cases would be in younger people and men.

The novel aspect of this paper is that the researchers have quantified the size of the problem for public health.

The results would suggest that in the UK, between 2010 and 2020, 2-6% of new cases of type 2 diabetes would be attributable to the consumption of sugar sweetened beverages. This figure is higher in the USA, where more sugar sweetened drinks are sold, estimated as 4-13% of new cases in the same period.

The publication of this study comes at a time when the WHO has recommended a reduction in the percentage of energy in our diet from sugar to less than 10%.[1] There is also a current political debate about whether taxing sugar sweetened drinks would be a way of modifying dietary intake in the UK. The potential impact of the predicted extra cases of type 2 diabetes on NHS resources adds to this debate.

Table 1

Association between consumption of sugar sweetened drinks, artificially sweetened drinks, and fruit juice and incident type 2 diabetes

Beverages	Relative risk†	95% CI
Sugar sweetened drinks	1.13	1.06 - 1.21
Artificially sweetened drinks	1.08	1.02 - 1.15
Fruit juices	1.07	1.01 - 1.14

†Adjusted for adiposity

DR MATTHEW LOCKYER

● **Imamura F, O'Connor L, Ye Z et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ* 2015;351:h3576**

REFERENCE

1 World Health Organization. Guideline: Sugars intake for adults and children. WHO. Geneva. 2015

Cardiovascular disease

Digoxin therapy associated with increased mortality in atrial fibrillation

The use of digoxin is independently associated with a raised risk of hospitalisation and death in adults with incident atrial fibrillation and no heart failure, a retrospective cohort study from the USA has found.

A total of 14,787 age, sex and high-dimensional propensity score-matched patients with incident atrial fibrillation and no previous heart failure or digoxin use were studied in the ATRIA-CVRN study.

The investigators looked at the association between newly initiated digoxin therapy and the risk of death and hospitalisation. The median follow-up was 1.17 years.

Digoxin use was associated with higher rates of death (8.3 vs 4.9 per 100 person-years; P < 0.001) and hospitalisation (60.1 vs 37.2 per 100 person-years; P < 0.001).

After adjustment for other factors the use of digoxin was associated with a 71% higher risk of death, hazard ratio (HR) 1.71 (95% CI: 1.52-1.93) and a 63% higher risk of hospitalisation, HR 1.63 (95% CI: 1.56-1.71).

No differences were found when the results were analysed by age or sex or using intention-to treat or on-treatment approaches.

Digoxin is still commonly used for rate control in atrial fibrillation and is particularly favoured in less active elderly patients where its relative inferiority in rate control relative to beta blockers and rate-limiting calcium antagonists is less noticeable. However, there is limited evidence supporting its use and previous studies have shown adverse outcomes.

The authors of this study conclude that in adults with atrial fibrillation, digoxin use was independently associated with higher risk of death and hospitalisation.

They recommend that other rate control options should be tried before resorting to digoxin and that this should generally be used with caution in the management of atrial fibrillation.

It is important to note that this trial did not include patients with atrial fibrillation and heart failure where there may still be a role for digoxin given its weakly positive inotropic action coupled with a beneficial effect on heart rate.

However, a recent systematic review and meta-analysis has also called this into question and it may be that the writing is on the wall for digoxin use after many years of relative security in guidelines and expert consensus.

DR PETER SAVILL

● **Freeman JV, Reynolds K, Fang M et al. Digoxin and risk of death in adults with atrial fibrillation: the ATRIA-CVRN study. *Circ Arrhythm Electrophysiol* 2015;8(1):49-58**

Addiction

Benzodiazepine use raises risk of fatal overdose in patients treated with opioid analgesics

The use of benzodiazepines is strongly associated with death from drug overdose in veterans receiving opioid analgesics, a study from the USA has found.

The authors compared historical data from 2,400 US veterans who had died from a drug overdose while receiving opioid analgesics with that of a random sample of nearly half a million (420,386) veterans who were known to have received opioid analgesia over a six-year period.

Patients prescribed methadone maintenance or those receiving palliative care were excluded.

Benzodiazepine prescribing history, dose, type and schedule were identified from the Veterans Health Administration database.

These data were linked to 'death from poisoning by any drug' from information contained in the National Death Index.

Of the 422,786 veterans who had received prescriptions for opioid analgesics, 112,069 (27%) had also received prescribed benzodiazepines during the study period.

Almost half (49%) of the deaths from drug overdose, 1,185, occurred when veterans had been prescribed opioids together with benzodiazepines. The adjusted hazard ratio (HR) was 2.33 (95% CI: 2.05-2.64) for former benzodiazepine prescription compared with no prescription and HR 3.86 (95% CI: 3.49-4.26) for »

current benzodiazepine prescription at the time of death compared with no prescription.

Risk of death increased as benzodiazepine daily dose increased. When compared with clonazepam, temazepam was associated with lower risk, HR 0.63 (95% CI: 0.46-0.82). All other benzodiazepines had a similar risk to clonazepam. There was no association between dosing schedule and risk of death.

Overdose from opioid analgesics is a significant cause of morbidity and mortality, and benzodiazepine use has been implicated as a risk factor for deaths from overdose of opioid analgesics.

This paper identifies a strong association between prescribed benzodiazepine use and death from drug overdose in patients receiving prescriptions for opioid analgesia.

The authors point out that as benzodiazepines are more likely to be prescribed to those with substance misuse and mental health problems, and that current prescribing may reflect more serious ongoing problems than those who had formerly received a prescription, confounding may exist.

They also note that the study applied to a mostly male cohort of veteran patients, and therefore data may not be able to be extrapolated to other populations.

However, GPs need to bear in mind that prescribed benzodiazepine use is a risk marker for death from overdose in their patients who are prescribed opioid analgesics. The authors suggest considering the option of providing naloxone for emergency use by carers in high-risk cases.

DR JEZ THOMPSON

● **Park TW, Saitz R, Ganoczy D et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350:h2698**

Sexual health

Is rapid HIV testing effective in primary care?

An educational outreach programme promoting opt-out rapid HIV testing of new practice registrants led to increased rates of HIV diagnosis but there was no significant difference in the proportion having low CD4 counts at diagnosis.

The study was based in Hackney, an area of London with a diagnosed HIV prevalence of 8 per 1,000. Practices were randomised into two groups.

The intervention group received a practice-based outreach educational programme with follow-up training, integrated rapid HIV testing into the registration health check, provided free rapid HIV tests and were paid £10 per test completed.

The control practices provided usual care which included HIV testing by serology opportunistically or at the patient's request. Hackney practices were incentivised to perform serological testing for HIV as part of sexual health checks and opportunistically when clinically indicated.

A pragmatic, cluster-randomised control trial design was used to see if the multifaceted educational outreach programme promoting rapid HIV testing in general practice would lead to increased and early detection of HIV.

The primary outcome was mean CD4 count of newly diagnosed patients; secondary outcomes were rate of new HIV diagnoses, percentage of patients with CD4 counts < 350 and percentage of patients with CD4 counts < 200. Women newly diagnosed through the UK Antenatal HIV Screening Programme were also included.

Overall 40 out of 45 practices agreed to take part. Three practices in the intervention group withdrew during the study but all provided complete study data which were included in the intention-to-treat analysis. Practice and population characteristics and the numbers of new registrants were similar at baseline.

The intervention group offered 11,187 rapid HIV tests and 4,978 (45%) were accepted by new registrants. Of these, 14 were reactive on rapid testing, including 11 that were confirmed HIV positive by serology and three confirmed HIV negative. Intervention practices also identified an additional 18 diagnoses through opportunistic serology compared with ten in the control practices.

Overall, intervention practices identified 32 new HIV-positive patients, whereas control practices identified 14 new cases.

CD4 count was available for 30 of 32 newly diagnosed patients from intervention practices and all of the 14 patients in control practices. Mean CD4 count was not significantly different between the two groups (356 vs 270, adjusted difference in square root transformed CD4 count 3.1 (95% CI: -1.2 to 7.4; P = 0.16).

Mean CD4 count was significantly different when antenatal screening was excluded 6.4 (95% CI: 1.2 to 11.6; P = 0.017) and when patients who were diagnosed with HIV but defaulted from care were included, the adjusted difference was 4.1 (95% CI: 0.0 to 8.1; P = 0.049).

The HIV diagnosis rate was 0.30 (95% CI: 0.11 to 0.85) per 10,000 patients per year in the intervention group and 0.07 (95% CI: 0.02 to 0.20) in the control group.

Nearly three quarters (73%) of patients in control practices had a CD4 count < 350 compared with just over half (55%) in intervention practices; the risk ratio was 0.75 (95% CI: 0.53 to 1.07). Just under half (46%) of patients from control practices had a CD4 count < 200 compared with 28% in intervention practices; risk ratio 0.60 (95% CI: 0.32 to 1.13).

Although the intervention led to increased rates of HIV diagnosis it did not produce significant differences in the proportion having low CD4 counts at diagnosis. It is worth noting that despite a combination of educational outreach and financial incentives, the number of HIV diagnoses was lower than expected.

Reducing the prevalence of undiagnosed HIV remains a challenge for the UK. Almost a quarter of the 107, 800 people with HIV are undiagnosed and 42% are diagnosed late (CD4 count < 350) and 24% very late (CD4 count < 200).

Earlier diagnosis can reduce morbidities related to low CD4 counts as well as risk of onward transmission.

NICE has already endorsed expansion of HIV testing especially in areas with high diagnosed prevalence of HIV (> 2 per 1,000). Pilot studies have demonstrated acceptability and feasibility of HIV testing in primary care but expanded testing has not been widely adopted in this setting.

Financial incentives and educational strategies are not the panacea to behaviour change in healthcare professionals especially in terms of health promotion and disease prevention. The jury is still out regarding the most effective strategy to encourage HIV testing in primary care. Perhaps we need to understand the motivation for primary care teams to deliver HIV testing.

DR RICHARD MA

● **Leber W, McMullen H, Anderson J et al. Promotion of rapid testing for HIV in primary care (RHIVA2): a cluster-randomised controlled trial. *Lancet HIV* dx.doi.org/10.1016/S2352-3018(15)00059-4**

Addiction

High rate of undiagnosed hepatitis C among current and former drug users

More than half of those who have ever injected drugs (PWID) in Scotland have hepatitis C (HCV) and six out of ten remain undiagnosed, a modelling study has estimated.

The authors set out to estimate the size and nature of the population of HCV-infected individuals among PWID in Scotland in 2009, both diagnosed and undiagnosed. They used the extensive data sets available in Scotland, including a drug misuse and a hepatitis C database and surveillance information from needle exchange schemes.

The authors estimated HCV antibody prevalence among PWID at 57% (95% credible interval (CI): 52-61%), corresponding to 46,657 cases (95% CI: 33,812-66, 803). Of these 59% were undiagnosed, representing 27,434 cases (95% CI: 14,636-47,564). Among the undiagnosed, 83% (95% CI: 75-89%) had not injected in the past year and 71% (95% CI: 58-85%) were aged 35-64 years.

This study demonstrates a high number of undiagnosed HCV-infected cases in Scotland. Undiagnosed status was particularly high among those who had not injected drugs for a year or more and who are more than 35 years old.

Chronic infection with HCV is a major cause of liver disease in the UK, which untreated may progress to cirrhosis and hepatocellular cancer. The most important vector for disease transmission is injecting drug use. Previous studies have indicated that the majority of those with HCV infection may be unaware of the diagnosis.

Targeting of screening and effective case finding are essential to reduce the burden of this disease, particularly as new developments in HCV antiviral treatments make them more effective, simpler and with fewer unwanted effects.

Case finding is essential both from the individual health and public health perspectives. Much of this will be undertaken in drug services. The study shows that a high proportion of undiagnosed cases are no longer injecting and are in an older age group, and so may no longer be in contact with drug services.

Doctors working in primary care may need to take a more active role in case finding. 'Targeting older individuals with a history of injecting drug use though primary care can also be an effective case-finding approach,' the authors state.

DR JEZ THOMPSON

● **Prevost TC, Presanis AM, Taylor A. Estimating the number of people with hepatitis C virus who have ever injected drugs and have yet to be diagnosed: an evidence synthesis approach for Scotland. *Addiction* 2015;110:1287-1300**

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