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RESEARCH NEWS All you need to read in the other general medical journals Alison Tonks, associate editor, *BMJ* atonsk@bmj.com

Genetic study confirms causal link between adiposity and cardiometabolic disease

A genetic predisposition to obesity is randomly allocated, and mendelian randomisation studies exploit this natural experiment to find out if well established associations between obesity and disease are likely to be causal. The latest study used a genetic variation that increases body mass index by 0.36 units per allele. In analyses pooling 36 observational studies, people with the implicated allele had a small but significantly increased risk of heart failure and the abnormal liver enzymes typical of non-alcoholic fatty liver disease. As expected, they also had an increased body mass index, and it's likely that the extra adiposity causes both heart failure and fatty liver, say the authors.

They confirmed similar links between the "fat" allele and diabetes, hypertension, metabolic syndrome, dyslipidaemia, and increased C reactive protein, a marker of inflammation. But they couldn't find a causal association between adiposity and heart disease, possibly because of low power. Genetic predisposition explains only a small fraction of the variation in body mass index, so studies have to be very big to find (or rule out) associations with disease. These authors had data on genotype, body mass index, and cardiometabolic outcomes in as many as 160 000 people, mostly from Europe. The effect of body mass index on most outcomes was similar when estimated with mendelian randomisation or with traditional observational methods.

PLoS Med 2013;10:e1001474

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Reassurance from Sweden about autism and IVF

Two and a half million infants were born in Sweden between 1982 and 2007, and close to 31 000 were conceived by in vitro fertilisation (IVF). A series of large scale analyses found no association between IVF and risk of autism in children and a weak association between IVF and mental retardation, which disappeared when researchers excluded multiple births.

Further exploration of different types of IVF suggested that intracytoplasmic sperm injection (ICSI) was associated with a higher risk of mental retarda-

tion than IVF without ICSI (adjusted relative risk 1.47, 95% CI 1.03 to 2.09; 90.6 v 60.8/100 000 person years). This association was weaker in singletons and stronger in infants born preterm. In Sweden, ICSI is generally reserved for couples with male factor infertility. The standard procedure, and reference for all comparative analyses, was IVF without ICSI combined with fresh embryo transfer.

All children in Sweden have a neurodevelopmental assessment at 4 years of age. The authors defined mental retardation as an IQ below 70 combined with limitations in adaptive behaviour. In autism analyses, they counted only children with a narrow definition of infantile or childhood autism, not wider autistic spectrum disorders.

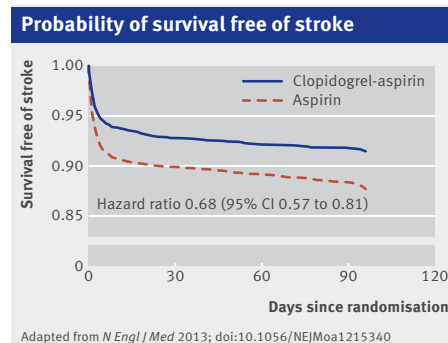
These new findings underline once again the importance of avoiding multiple pregnancies and preterm deliveries after IVF, says a linked editorial (p 42). But they don't rule out small independent risks associated with ICSI, so long term surveillance should continue.

JAMA 2013;310:75-84

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Early dual therapy for Chinese adults with TIA

Stroke is common in the weeks after a minor cerebral ischaemic event such as transient ischaemic attack (TIA). Antiplatelet therapy can help reduce the risk, and the combination of aspirin and clopidogrel worked better than aspirin alone in a recent trial from China. Dual therapy with aspirin plus clopidogrel for the first 21 days, followed by clopidogrel alone to day 90, prevented one new stroke for every 29 adults treated (incidence 8.2% v 11.7%; hazard ratio 0.68, 95% CI 0.57 to 0.81) when compared with aspirin for the full 90 days. Dual therapy did not increase the risk of moderate or severe bleeding, or haemorrhagic stroke (0.3% v 0.3%).



Two thirds of participants were hypertensive, and more than 40% were smokers or ex smokers (2221/5170). They had a high risk of recurrence, a low risk of bleeding, and began treatment less than 24 hours after a TIA or minor ischaemic stroke. These events should be treated as a medical emergency in Chinese patients with similar clinical profiles, says a linked editorial (doi:10.1056/NEJMe1305127). But doctors should be careful not to generalise too widely, not least because metabolism of clopidogrel has a genetic element that is different for populations inside and outside of China.

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Antipsychotics ranked by effectiveness and side effects

A comprehensive review of antipsychotic drug treatments for schizophrenia has ranked 15 agents in order of effectiveness and side effects. The authors hope that their rankings, derived from a network meta-analysis of 212 mostly placebo controlled trials, will help doctors and patients choose a drug with the best profile for each individual. All agents were more effective than placebo, and differences between treatments were small but potentially noticeable (standardised mean differences in effectiveness 0.11 to 0.55). Clozapine, amisulpride, and olanzapine were among the most effective agents; iloperidone and lurasidone were among the least effective. All had very different side effects. The authors looked at discontinuation (for any reason), weight gain, sedation, extrapyramidal side effects, and each drug's impact on serum prolactin and QTc interval. The rankings were different for each outcome and broadly confirmed that the more effective drugs also tended to have more side effects. Amisulpride, for example, was one of the worst agents for prolonging the QTc interval and clozapine caused the worst sedation.

Network meta-analyses have many limitations and these rankings can only ever be a rough guide, says a linked comment (doi:10.1016/S0140-6736(13)61032-6). Large head to head trials comparing agents directly are always better, but they are rarely done because regulators don't demand comparative evidence before licensing.

Lancet 2013; doi:10.1016/S0140-6736(13)60733-3

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