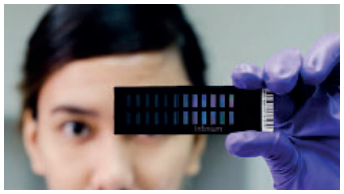
research

Antihypertensive treatment and risk of falls and other adverse events p 271



Genotyping of rare pathogenic variants using SNP chips p 272

Trends of hospital admissions in the UK due to food induced anaphylaxis p 274

ORIGINAL RESEARCH Systematic review and meta-analysis

Association between antihypertensive treatment and adverse events

Albasri A, Hattle M, Koshiaris C, et al; on behalf of the STRATIFY investigators

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Find this at: http://dx.doi.org/10.1136/bmj.n189

Study question What is the association between antihypertensive treatment and specific adverse events?

Methods This was a systematic review and meta-analysis of randomised controlled trials. Studies were eligible for inclusion if they examined adults receiving antihypertensive treatment compared with placebo or no treatment, more antihypertensive drugs compared with fewer antihypertensive drugs, or higher blood pressure targets compared with lower targets. The primary outcome was falls. Secondary outcomes included acute kidney injury, fractures, gout, hyperkalaemia, hypokalaemia, hypotension, and syncope. Random effects meta-analysis was used to determine pooled treatment effects.

Study answer and limitations 58 randomised controlled trials were identified, including 280 638 participants followed up for a median of 3 (interquartile range 2-4) years. Among seven trials, no evidence was found of an association between antihypertensive treatment and falls (summary risk ratio 1.05, 95% confidence interval 0.89 to 1.24, τ^2=0.009). Antihypertensives were associated with an increased risk of acute kidney injury (1.18, 95% confidence interval 1.01 to 1.39, τ^2=0.037), hyperkalaemia (1.89, 1.56 to 2.30, τ^2=0.122), hypotension (1.97, 1.67 to 2.32, τ^2=0.132), and syncope (1.28, 1.03 to 1.59, τ^2=0.050). The heterogeneity between studies assessing acute kidney injury and hyperkalaemia events was reduced when focusing on drugs that affect the renin-angiotensin-aldosterone system, suggesting that these effects might be drug specific. The review was limited to studies that reported adverse events. The accuracy of this reporting was unclear.

What this study adds No evidence was found to suggest that antihypertensive treatment is associated with falls, but evidence did suggest an association with mild (hyperkalaemia, hypotension) or severe or severe (acute kidney injury, syncope) adverse events, some of which were drug class specific. These data could be used to inform shared decision making between doctors and patients about initiation and continuation of antihypertensive treatment, especially in patients at high risk of harm because of previous adverse events or poor renal function.

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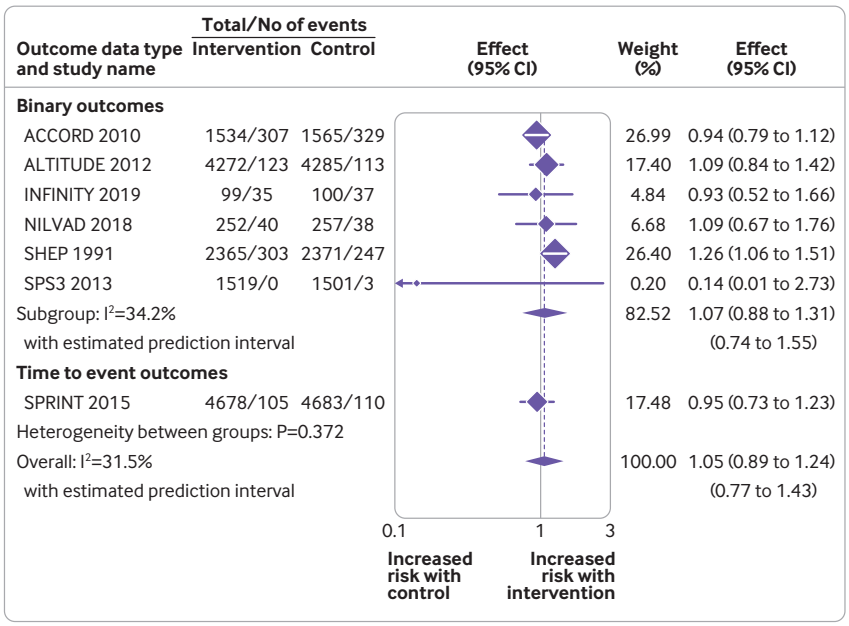
Study registration PROSPERO CRD42018116860.



Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and falls

Genetic testing for rare pathogenic variants

ORIGINAL RESEARCH Retrospective, population based diagnostic evaluation

Use of SNP chips to detect rare pathogenic variants

Weedon MN, Jackson L, Harrison JW, et al

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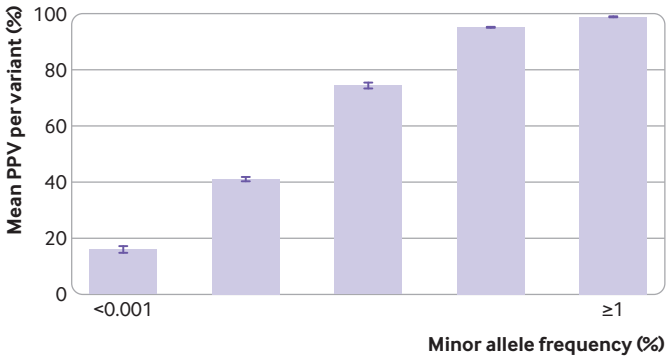
Study question Are the sensitivity and specificity of single nucleotide polymorphism (SNP) chips adequate for detecting rare pathogenic variants in a clinically unselected population?



Positive predictive value (PPV) of UK Biobank Axiom SNP chip for detecting variants at different population frequencies

Methods This study compared genotypes from SNP chips (index test) with next generation sequencing data (reference standard) in 49 908 participants in the UK Biobank and an additional 21 people who purchased consumer genetic tests and shared their data online through the Personal Genome Project. Genotyping (identification of the correct DNA base at a specific genomic location) using SNP chips versus sequencing was evaluated, and the results were split by frequency of that genotype in the population. Rare pathogenic variants in well established disease-causing genes were then used as exemplars for detailed analysis of clinically actionable variants in the UK Biobank, and the relevant health related outcomes in participants were assessed.

Study answer and limitations Overall, genotyping using SNP chips performed well compared with sequencing. However, SNP

BMJ OPINION Caroline Wright and Michael Weedon

SNP chips perform poorly for detecting very rare genetic variants

We are both geneticists interested in finding and understanding diseases caused by rare genetic variants. Genetic testing for these rare diseases can have profound clinical impact. For example, women with a rare pathogenic variant in the *BRCA1* or *BRCA2* genes may be advised to undergo bilateral prophylactic mastectomy.

A few years ago, we heard anecdotes from clinicians about patients who had received false positive results that had been used to schedule invasive medical procedures that were both unnecessary and unwarranted. False positive results from single nucleotide polymorphism (SNP) chips for very rare genetic variants had also started to appear in the published literature. SNP chips are DNA microarrays originally designed to assay common genetic variants across the genome that are present in more than one in 100 people. They have been successfully used in genome-wide association studies and consumer genomic testing for over a decade. However, they have increasingly been used to assay thousands of rare genetic variants, which are much more challenging to genotype accurately using SNP chip technology, resulting in an increase in false positive test results—that is, when the genetic variant identified is not present in the individual.

Although the challenges of reliably detecting rare variants using SNP chips were known within the genetics community, we were surprised to find that a systematic evaluation of the performance of this assay had not been published. Because SNP chips are such a widely used and high performing assay for common genetic variants, we were also surprised that the differing performance of SNP chips for detecting rare variants was not well appreciated in the wider research or medical communities. Fortunately, we had recently received both SNP chip and genome-wide DNA sequencing data on 50 000 individuals through the UK Biobank—a population cohort of adult volunteers from across the UK. This large dataset allowed us to investigate systematically the performance of SNP chips across millions of genetic variants with a wide range of frequencies, down to those present in fewer than one in 50 000 individuals.

A very rare, disease-causing variant detected using a SNP chip is more likely to be wrong than right

As expected, we found that although the SNP chips performed well for most (common) variants, they performed much less well for rare variants, with low positive predictive values of around 16% for very rare variants in the UK Biobank. Knowing that this result would likely vary with the design and manufacture of different SNP chips, as well as the quality of the sequencing data, we replicated our analysis in a small group of individuals who had shared their consumer genomics data online through the Personal Genome Project. We found that nearly every individual had at least one rare disease-causing variant that was falsely detected by the SNP chip. According to our research, it seems that a very rare, disease-causing variant detected using a SNP chip is more likely to be wrong than right. Although some consumer genomics companies perform sequencing to validate important results before releasing them to consumers, most consumers also download their "raw" SNP chip data for secondary analysis, and these raw data still contain the erroneous results.

The implications of our findings are simple: SNP chips perform poorly for detecting very rare genetic variants and the results should not be used in clinical practice without validation.

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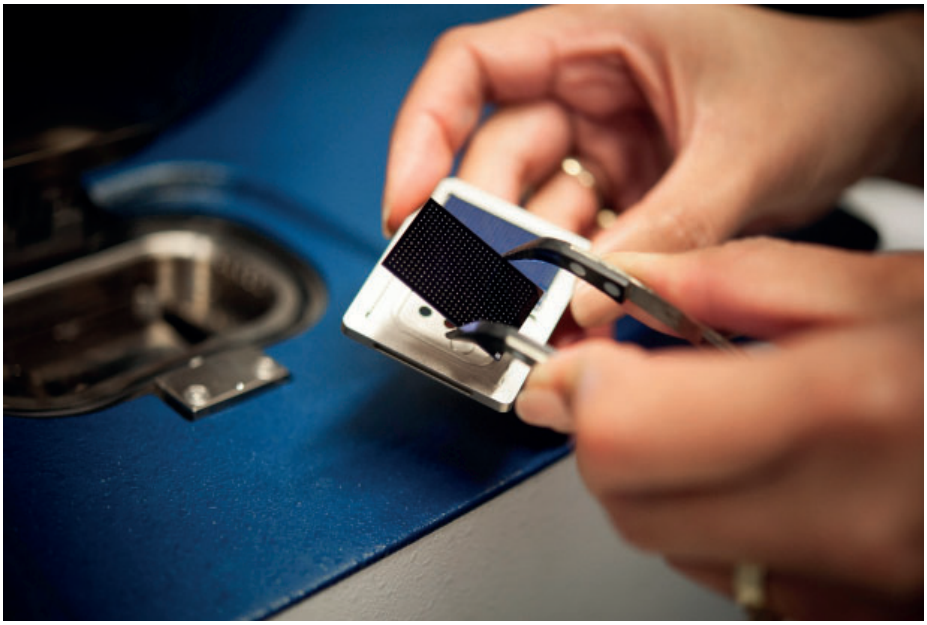
chips had a low positive predictive value of less than 16% for detecting very rare variants in the UK Biobank. Most variants with population frequency below 0.001% were false positives. A similar performance was seen in a small sample of raw SNP chip data from consumer genetic tests. The study was limited to the genotyping array and sequencing platforms used in the UK Biobank and Personal Genome Project data.

What this study adds This systematic evaluation shows that SNP chips are unreliable for genotyping very rare pathogenic variants and should not be used to guide health decisions without validation.

Funding, competing interests, and data sharing
No specific funding was received for this study. The authors have no competing interests. Data are available from the UK Biobank and Personal Genome Project websites



Food induced anaphylaxis in the UK

Baseggio Conrado A, Ierodiakonou D, Gowland MH, et al

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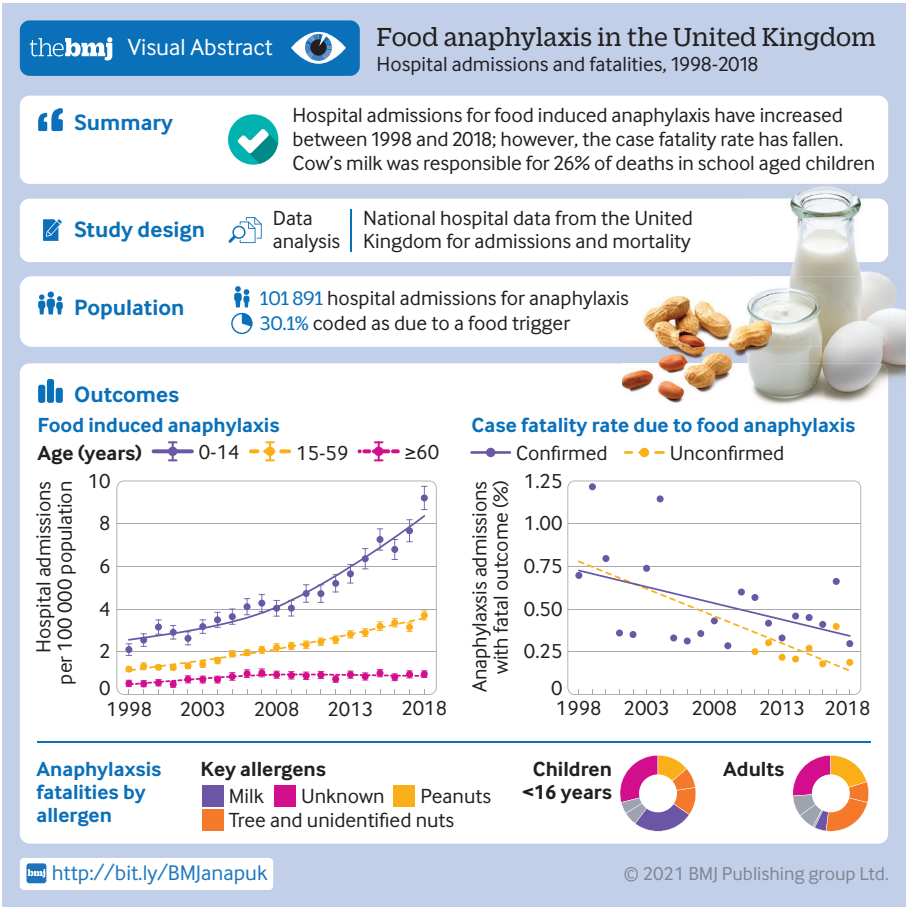
Study question What are the time trends for hospital admissions due to food induced anaphylaxis in the United Kingdom over the past 20 years?

Methods Data were extracted from national UK datasets relating to hospital admissions for anaphylaxis from 1998 to 2018. Anaphylaxis fatality data were obtained from the UK Fatal Anaphylaxis Register. Time trends for hospital admissions due to non-food and food induced anaphylaxis were analysed for the UK as a whole and for devolved nations (England, Scotland, Wales, and Northern Ireland). These trends in admission rates were examined alongside the case fatality rate (number of fatalities as a proportion of hospital admissions). Annual prescription data for adrenaline autoinjectors were also analysed.

Study answer and limitations Between 1998 and 2018, 101 891 people were admitted to hospital for anaphylaxis. Of these admissions, 30 700 (30.1%) were coded as due to a food trigger. Food anaphylaxis admissions increased from 1.23 to 4.04 per 100 000 population per year (from 1998 to 2018), an annual increase of 5.7% (95% confidence interval 5.5% to 5.9%, P<0.001). The largest increase in hospital admissions was observed in children younger than 15 years, with an increase from 2.1 to 9.2 admissions per 100 000 population per year (an annual increase of 6.6%, 6.3% to 7.0%). For comparison, the annual increase was 5.9% (5.6% to 6.2%) in people aged 15-59 years and 2.1% (1.8% to 3.1%) in those aged 60 years and older. 152 deaths were identified in which the fatal event was probably caused by food induced anaphylaxis. The case fatality rate decreased from 0.7% to 0.19% for confirmed fatal food anaphylaxis (rate ratio 0.931, 95% confidence interval 0.904 to 0.959, P<0.001) and to 0.30% for suspected fatal food anaphylaxis (0.970, 0.945 to 0.996, P=0.024). At least 46% (86 of 187, which also includes 35 deaths in 1992-98) of deaths were triggered by peanuts or tree nuts. Cow's milk was responsible for 26% (17 of 66) of deaths in school aged children. Over the same period, prescriptions for adrenaline autoinjectors increased by 336% (rate ratio 1.113, 1.112 to 1.113; an increase of 11% per year). While the use of national datasets provides a unique opportunity to draw conclusions, these data are limited by potential miscoding.

What this study adds Hospital admissions for food induced anaphylaxis have increased between 1998 and 2018; however, the case fatality rate has fallen. In school aged children, cow's milk is now the most common single cause of fatal anaphylaxis.

Funding, competing interests, and data sharing
Funded by the UK Medical Research Council and the UK Food Standards Agency.
See full paper on bmj.com for competing interests.
Requests for data can be made to the corresponding author (p.turner@imperial.ac.uk).



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