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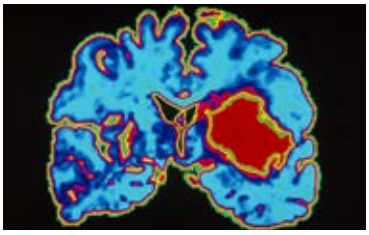

Higher rates of stroke but lower rates of mortality in older people with CKD and AF started on anticoagulants p 269

Consumption of ultra-processed foods may increase the risk of cancer p 270

Data availability remains suboptimal in journals with a full data sharing policy p 272

ORIGINAL RESEARCH Population based study in UK primary care

Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation

Kumar S, de Lusignan S, McGovern A, et al

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Find this at: http://dx.doi.org/10.1136/bmj.k342

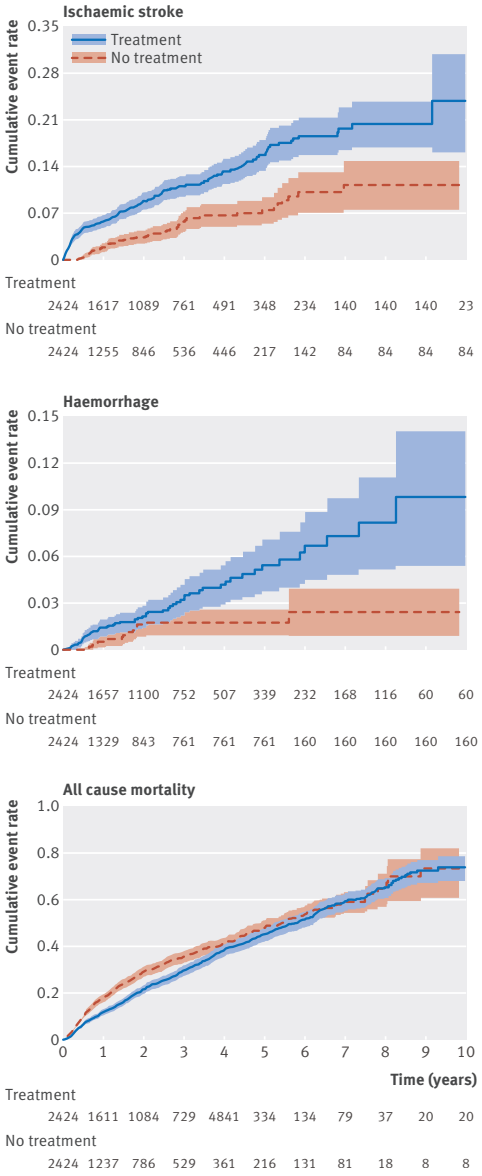
Study question What is the association between anticoagulation, ischaemic stroke, gastrointestinal and cerebral haemorrhage, and all cause mortality in older people with chronic kidney disease and new onset atrial fibrillation?

Methods The authors conducted a propensity matched, population based, retrospective cohort analysis from January 2006 to December 2016, using the Royal College of General Practitioners' Research and Surveillance Centre database population of almost 2.73 million patients from 110 general practices across England and Wales. Patients aged 65 years and over with newly diagnosed atrial fibrillation and estimated glomerular filtration rate of <50 mL/min/1.73m^2, calculated using the chronic kidney disease epidemiology collaboration creatinine equation, were included.

Study answer and limitations 6977 patients with chronic kidney disease and newly diagnosed atrial fibrillation were identified, 2434 of whom were started on anticoagulant drugs within 60 days of diagnosis, and 4543 were not. 2434 pairs were matched using propensity scores by exposure to anticoagulant or none and followed for a median of 506 days. The hazard ratios for ischaemic stroke, haemorrhage, and all cause mortality for those using anticoagulants were 2.60 (95% confidence interval 2.00 to 3.38), 2.42 (1.44 to 4.05), and 0.82 (0.74 to 0.91), respectively, compared with those who received no anticoagulant. Despite well matched groups after propensity score matching, the reported associations may have been confounded by indication.

What this study adds In older people with concomitant atrial fibrillation and chronic kidney disease, taking anticoagulant drugs was associated with a higher rate of ischaemic stroke and haemorrhage but a paradoxically lower rate of all cause mortality. There is an urgent need for adequately powered randomised controlled trials to provide clarity on the optimal clinical management of this challenging patient group.

Funding, competing interests, data sharing Two authors report institutional grants and personal fees related to advice to various drug companies and research bodies. Full details are on bmj.com. Data sharing is not possible.



Kaplan-Meier survival curve by anticoagulation treatment status

Ultra-processed foods and cancer

ORIGINAL RESEARCH Results from NutriNet-Santé prospective cohort

Consumption of ultra-processed foods and cancer risk

Fiolet T, Srour B, Sellem L, et al

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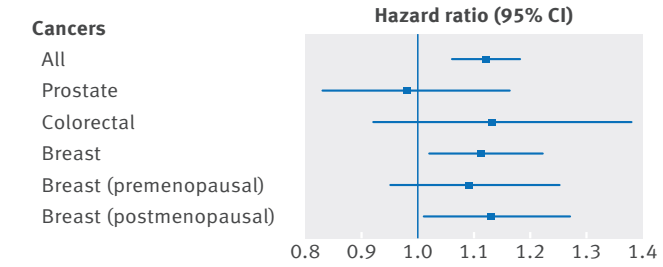
Find this at: http://dx.doi.org/10.1136/bmj.k322

Study question What are the associations between consumption of ultra-processed food and risk of cancer?

Methods This was a population based cohort study including 104 980 participants aged 18 years or more (mean age 42.8 years) from the French NutriNet-Santé cohort (2009-17). Dietary intakes were collected using repeated 24 hour dietary records designed to register participants' usual consumption for 3300 different food items. These items were categorised according to their degree of processing according to the NOVA classification. Associations between intake of ultra-processed foods and risks of overall, breast, prostate, and colorectal cancer were assessed by multivariable Cox proportional hazard models adjusted for known risk factors.

Study answer and limitations A 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer (hazard ratio 1.12 (95% confidence interval 1.06 to 1.18), P for trend<0.001, 2228 cases for overall cancer; 1.11 (1.02 to 1.22), P for trend=0.02, 739 cases for breast cancer). These results remained statistically significant

Hazard ratios (with 95% CIs) for cancer for an increase of 10% in proportion of ultra-processed food in diet



COMMENTARY The possibility of a link deserves further careful exploration

In this issue of *The BMJ*, Fiolet and colleagues report an association between intake of ultra-processed food and incidence of total cancer and breast cancer.[1] They used data from a population based prospective cohort of 104 980 middle aged French women and men. This web based cohort study regularly evaluates habitual dietary intake through repeated dietary recalls, uses novel research methods to bypass the increasing challenges in recruiting and retaining study participants, and efficiently uses administrative data to validate cancer outcomes.

As the global consumption of highly processed foods increases,[2] understanding the health impact of these foods has become a relevant and timely topic. Results from this study support the claim that the shift in the world's food supply to highly processed foods may partly account for increasing trends in the incidence of non-communicable diseases, including cancer.[3]

Given the complexity in defining the precise exposures relevant to cancer, as well as the methodological challenges associated with observational research, results from Fiolet and colleagues' analysis should be viewed as an initial step towards understanding the potential effect of processed foods on the health of human populations.

> We are a long way from understanding the full implications of food processing for health and wellbeing

Difficult questions

Firstly, "ultra-processed foods" is a broad category that includes multiple foods prepared by a variety of methods and containing myriad nutrients and food additives. Such a broadly defined exposure affects the interpretation of results from epidemiological analyses. What is the actual causal effect being estimated? Is the exposure causing the disease a specific food group (such as sugary products)? Or is it a macronutrient (such as fat)? Is it a food contaminant from packaging? What are the potential carcinogenic mechanisms driving the observed association?

The authors grouped foods into four food processing categories,[4] including ultra-processed foods, based on "the nature, extent, and purpose of the industrial processing." Although the classification may be useful for descriptive purposes and for replication, this approach may not provide sufficient detail for consumers and decision makers in public health. Accordingly, the authors evaluated different food groups and found no evidence that the overall association was driven by a specific food subgroup such as starchy foods. However, to quantify the effect of food processing on health accurately, we need to refine the causal question further by identifying more precisely the ultra-processed foods that could lead to cancer.

Secondly, as with any observational study, confounding by unknown factors common to consumption of ultra-processed foods and cancer cannot be excluded. Fiolet and colleagues adjusted their analyses for several well known risk factors for cancer, some of which seemed to be strongly related to ultra-processed food consumption. For example, cigarette smoking and low physical activity were far more common in participants who consumed a larger proportion of ultra-processed foods.

Given the relatively weak association between intake of ultra-processed foods and incidence of cancer, and the known difficulties in measuring some important risk factors for cancer such as physical activity, the possibility of residual confounding remains.

The ultimate goal of nutritional epidemiology is to generate evidence to provide sound actionable advice to

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after adjustment for several markers of the nutritional quality of the diet. This study was observational, so causality of the observed associations cannot be established. Caution is needed in the extrapolation of the results from a cohort of volunteers to the whole general population.

What this study adds Consumption of ultra-processed foods may increase the risk of cancer. Further studies are needed to investigate these associations in the longer term and to better understand the relative effect of the various dimensions of processing (nutritional composition, food additives, contact materials, and neoformed contaminants) in these relations.

Funding, competing interests, data sharing This study was supported by public institutions only.
Study registration Clinicaltrials.gov NCT03335644.

individuals and shape evidence based public policy to lower the risk of disease and increase wellbeing. Fiolet and colleagues provide an initial insight into a possible link between ultra-processed food related exposures and cancer. The authors should be commended for collecting detailed dietary and cancer data and for conducting multiple secondary and sensitivity analyses to test different assumptions. Their interesting results require replication and further refinement.

Back to basics

The changing realities of the global food supply and the inherent limitations of epidemiological studies call for more basic science, including data from animals, to inform further research on the effect of food processing on humans. We are a long way from understanding the full implications of food processing for health and wellbeing. Care should be taken to transmit the strengths and limitations of this latest analysis to the general public and to increase the public's understanding of the complexity associated with nutritional research in free living populations.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k599

A 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer

Data sharing in medical research

ORIGINAL RESEARCH Survey of studies published in *The BMJ* and *PLOS Medicine*

Data sharing and reanalysis of randomised controlled trials in leading biomedical journals with a full data sharing policy

Naudet F, Sakarovitch C, Janiaud P, et al

Cite this as: *BMJ* 2018;360:k400
Find this at: http://dx.doi.org/10.1136/bmj.k400

Study question How effective is data sharing of randomised controlled trials in journals with a full data sharing policy?

Methods In this study the authors searched PubMed/Medline for randomised controlled trials that had been submitted and published by *The BMJ* and *PLOS Medicine* subsequent to the adoption of data sharing policies by these journals. Data availability was defined as the eventual receipt of complete data with clear labelling. All primary outcomes were then reanalysed to assess to what extent studies were reproduced.

Study answer and limitations 37 randomised controlled trials (21 from *The BMJ* and 16 from *PLOS Medicine*) published between 2013 and 2016 met the eligibility criteria. 17 (46%, 95% confidence interval 30% to 62%) trials satisfied the authors' definition of data availability and 14 of the 17 (82%, 59% to 94%) were fully reproduced on all their primary outcomes. Of the remaining, errors occurred in two papers but reached similar conclusions, and one paper did not provide enough information in the methods section to reproduce the analyses. Difficulties were identified, such as problems in contacting corresponding authors and lack of resources on their behalf in preparing the datasets. The data sharing policies mandate data sharing upon "reasonable request," and it is possible that authors did not perceive the current authors' request, done for an audit, to be reasonable.

What this study adds Data availability was not optimal in journals with a full data sharing policy, but the 46% data sharing rate observed is much higher than elsewhere in the biomedical literature. When reanalyses are possible, these mostly yield similar results to the original analysis.

Funding, competing interests, data sharing The Meta-Research Innovation Center at Stanford has been fundedby Laura and John Arnold Foundation but there was no direct funding for this study. The authors have no relevant competing interests. Data are shared on the Open Science Framework (https://osf.io/jgsw3/).
Study registration Open Science Framework osf.io/c4zke.

COMMENTARY Trust is the elephant in the room

There is a growing consensus that data sharing is an inseparable part of the research process.[1 2] My publicly stated position is that an investigator who performs studies in people has implicitly agreed to a social contract, which includes the responsibility to make the raw data available for examination.[3] It has always been delusional for researchers to imagine that clinicians and the public would believe their findings and accept their conclusions without access to supporting data.

Why have some researchers resisted? Cynics have hypothesised that the research community must have something to hide; that if examined, unpublished raw data would not corroborate published findings. Such broad based suspiciousness has been counterproductive. Many investigators who might otherwise have been open to data sharing have felt compelled to resist the policy, fearing its primary purpose might be to conduct (what they considered to be) a "witch hunt."

In this issue, Naudet and colleagues explored whether researchers who had agreed to data sharing would actually keep their end of the bargain.[2] They requested individual patient data from the authors of 37 clinical trials that were published under an explicit agreement to share data. Analysable datasets were returned in a timely manner about half the time.

In one instance, researchers stated that they did not endorse data sharing for the purposes of the study—"to explore the effectiveness of data sharing." Providing access to data requires considerable time and effort. Some may have balked at the notion of doing a great deal of work, simply to allow someone the opportunity to verify their results.

Cynics have hypothesised that the research community must have something to hide

Trust is the crux of the matter. Some researchers who did not provide datasets may have been sceptical of Naudet and colleagues' motives; meanwhile, Naudet and colleagues may have harboured subconscious doubts about the researchers' claim that their raw data would support their findings. Interestingly, most of their audits verified the primary conclusions of the researchers' work.

How do we build trust? Everyone who submits research for the public good should naturally expect that they will be asked to make their data available for examination and reanalysis. This is not a new idea. Citizens who pay taxes assume that some federal agency is poised to check their calculations. In the US, every pharmaceutical company that submits an application to the Food and Drug Administration for a new chemical entity does so with the full understanding that their raw data will be audited and their analyses verified.

Naudet and colleagues highlight the ultimate dream of data sharing—that reuse might translate into discoveries that can change care without generating false positive findings. However, this lofty aim will never be realised if we do not recognise the elephant in the room—the mutual lack of trust between researchers and the communities they serve.

A requirement for data sharing might sound like progress, but its implementation is complicated, costly, and may be onerous; it will take time to work out the ethos and the mechanics of the process. Yet we will not be able meaningfully to tackle any of the procedural issues if we do not first find a way to inspire confidence in each other. Without that, data sharing will become a weapon for the sceptics rather than a conduit for the advancement of science and medicine.

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