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Implausible results in human nutrition research

Definitive solutions won't come from another million observational papers or small randomised trials

John P A Ioannidis professor of medicine, health research and policy, and statistics, Stanford Prevention Research Center, Stanford, CA 94305, USA jioannid@stanford.edu

Research into human nutrition has been criticised on many occasions. Critics have focused on the poor track record of observational claims when tested in subsequent randomised trials (0/52 success rate in one review).[1-3] In contrast to major nutritional deficiencies and extreme cases, the effects of modest differences in nutrient intake have been difficult to study reliably at the population level. Nonetheless, some results, even of randomised trials, have been extremely promising.[4 5] However, to establish a less controversial legacy for this important field, we should avoid past traps and be explicit about reasonable expectations. Implausible results that are "too good to be true" still threaten nutritional research on many fronts, including survey measurements, observational associations, treatment effects in randomised trials, and estimates of the impact on populations.

Nutritional intake is notoriously difficult to capture with the questionnaire methods used by most studies. A recent analysis showed that in the National Health and Nutrition Examination Survey, an otherwise superb study, for two thirds of the participants the energy intake measures inferred from the questionnaire are incompatible with life.[6] More sophisticated measurements based on biochemical, web, camera, mobile, or sensor tools may not necessarily reduce bias.[7] Caution about the reliability of measurements should extend to inferences that depend on them.

Almost every single nutrient has peer reviewed publications associating it with almost any outcome.[8] On 25 October 2013, PubMed listed 34 291 papers with the keywords "coffee OR caffeine" and 12 741 with "soy," many of which referred to associations. In this literature of epidemic proportions, how many results are correct?

Many findings are entirely implausible. Relative risks that suggest we can halve the burden of cancer with just a couple of servings a day of a single nutrient still circulate widely in peer reviewed journals.[8] However, on the basis of dozens of randomised trials, single nutrients are unlikely to have relative risks less than 0.90 for major clinical outcomes when extreme tertiles of population intake are compared—most are greater than 0.95.[9] For overall mortality, relative risks are typically greater than 0.995, if not entirely null. The respective absolute risk differences would be trivial. Observational studies and even randomised trials of single nutrients seem hopeless, with rare exceptions. Even minimal confounding or other biases create noise that exceeds any genuine effect. Big datasets just confer spurious precision status to noise.

Larger effect sizes are more plausible for complex dietary patterns that sum the effects of multiple nutrients and behaviours. Indeed, some randomised trials have shown interesting results. The Lyon Diet Heart study and recently the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) trial showed 70% and 30% relative risk reductions, respectively,[4 5] in composite clinical outcomes with Mediterranean diets. These effect sizes are probably greatly exaggerated. The early termination of these trials owing to statistically significant interim analyses inflates estimates of treatment effects.[10] Other reasons for inflated effects include the selection of high risk populations (patients with heart disease and metabolic syndrome, respectively) and invalid comparator diets in control arms (in PREDIMED, 37% of energy came from fat in the "low fat" control arm, whereas low fat is defined as <10%). Inflated effects can also be caused by arm imbalances despite randomisation and unavoidable unmasked designs that may affect ascertainment of clinical outcomes. PREDIMED data are also supporting a rapidly growing factory of secondary publications, many of which present grossly implausible observational claims—for example, eating more than three servings of nuts a week cuts overall mortality by 39%.[11]


DAUMIER

Despite the hype, these randomised trials represent a major step forward. They offer hope that we could identify nutrition related interventions that produce a 5-10% relative risk reduction in overall mortality in the general population, not just in high risk patients. However, such studies would require more than 10 times the sample size of PREDIMED (n=7447 participants), long term follow-up, linkage to death registries, and careful efforts to maximise adherence. Interventions may consider not only nutritional patterns, but also factors that affect lifestyle and adherence. Trial sponsoring and conduct should be free of conflicts that favour nutritional products or diets. Given that fanatical opinions abound in nutrition, allegiance bias should also be minimised.

According to the latest burden of disease study,[12] 26% of deaths and 14% of disability adjusted life years in the United States are attributed to dietary risk factors, without counting the impact of obesity. No other risk factor comes close to diet in these calculations (not even tobacco and physical inactivity). I suspect this is another implausible result. It builds on risk estimates from the same data of largely implausible nutritional studies discussed above. Moreover, socioeconomic factors are not considered, although they may be at the root of health problems. Poor diet may partly be a correlate or one of several paths through which social factors operate on health.

Even if the impact of dietary risks is one tenth of that suggested by the burden of disease study,[12] it still deserves attention. Definitive solutions will not come from another million observational papers or a few small randomised trials. Randomised trials are needed mainly to inform the design of pivotal mega-trials of comprehensive interventions. We should also continue to explore other aspects of food and nutrition—such as food security, sustainability, social inequalities, famine, and impact of food production on climate change—that may also affect human societies and wellbeing through multiple pathways. Food and nutrition may well make a major difference, but perhaps for reasons other than those that are usually touted, debated about, and contradicted.

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This lack of effect confirms the results of two similar pilot studies in patients with COPD, as well as recent trials of telemonitoring in heart failure

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Telemonitoring for patients with chronic obstructive pulmonary disease

Adds little to well supported self management

Rachel Jordan senior lecturer, School of Health and Population Sciences, University of Birmingham, Birmingham B15 2TT, UK r.e.jordan@bham.ac.uk
Peymane Adab professor, School of Health and Population Sciences, University of Birmingham, Birmingham B15 2TT, UK
Kate Jolly professor, School of Health and Population Sciences, University of Birmingham, Birmingham B15 2TT, UK

Telemonitoring has been promoted as a solution to the management of rising numbers of patients worldwide with long term health problems. Although there is some evidence that such interventions empower patients to change behaviour, their effect on clinical outcomes is not clear.[1] In a linked paper (p 12), Pinnock and colleagues report the results of their telemonitoring trial in 256 patients with chronic obstructive pulmonary disease (COPD) admitted to hospital in the previous year with an exacerbation.[2]

Patients with COPD are encouraged to self manage their disease by recognising exacerbations and self medicating to limit the impact of an exacerbation (action planning), thus avoiding admission. Cochrane systematic reviews conclude that education on self management is associated with a reduced risk of hospital admission,[3] although action plans with limited education have no effect.[4]

Another approach is the telemonitoring of patients' symptoms by a remote clinical team. Systematic reviews highlight the heterogeneity of interventions and the difficulty in isolating the telemonitoring package from the remaining elements of the service.[5 6] In Pinnock and colleagues' trial in Lothian,[2] patients were randomised to the telemonitoring or conventional self monitoring group. All patients received self management advice—education on self management of exacerbations reinforced with the British Lung Foundation booklet, a written management plan, and an emergency supply of drugs, integrated within the standard clinical care service for their region.

The novelty of this trial is the addition in the intervention arm of telemonitoring alone to background self management and clinical support. In contrast to previous trials, this allowed the effects of telemonitoring to be separated from the effects of existing services. The package consisted of touch screen operated daily questionnaires about symptoms and drug use, with an instrument to measure oxygen saturation. Data were transmitted daily by an internet connection to the clinical monitoring team, which contacted patients whose score reached a validated threshold. Clinicians responded by advising rescue drugs, a home visit, admission to hospital, or further review. Eighty five per cent (109/128) of patients randomised to the intervention received the equipment and completed the training, which was impressive given the inevitable logistical difficulties with installation.


"By the pricking of my thumbs"

After 12 months, no difference was seen in hospital admissions for COPD between the two groups (hazard ratio 0.98, 95% confidence interval 0.66 to 1.44). Furthermore, no differences were seen in health related quality of life, anxiety or depression, self efficacy, knowledge, or adherence to drugs. This lack of effect confirms the results of two similar pilot studies in patients with COPD,[7 8] as well as recent trials of telemonitoring in heart failure.[9 10]

So why didn't it work? Usually self recording and feedback can help change behaviour. But here the clinicians made the decisions. Did the patients, having passed on their information, also pass on the responsibility for managing exacerbations?

There were large numbers of contacts through the alert system (24/person/year). Although it is not clear how many of these were "false alarms," only 1.1 hospital visits per person were instigated. This low threshold should have been sensitive enough to help patients who truly needed advice. Contacts not related to alerts were also higher in the intervention arm, suggesting that routine support in this group may have been more proactive.

Background levels of self management support and care seemed high for at least two of the regions, and this may not have allowed for the monitoring system to show any additional benefit. Education about self management was optimised in both arms before randomisation; if this had been more rigorous than usual care, it may have been partly responsible for reducing admissions overall. However, without a true usual care group this is not clear. Notably, the rate of exacerbations in the control arm (12.8/patient/year) was more than four times the expected level.[11] This suggests that all patients were receiving a high level of proactive care or self managing well, or that the questionnaires were unusually sensitive (or a combination of both).

A more targeted approach could focus on "poor self managers." However, there were no data to describe how well different types of patient adhered to daily telemonitoring and limited evidence from subgroup analyses of individuals who might respond better. Counterintuitively, patients with milder disease and those with higher depression scores seemed to have higher admission rates with telemonitoring. Telemonitoring may also have picked up milder exacerbations not usually reported by patients.

What are the implications for the management of COPD? This trial suggests that the addition of telemonitoring to the management of high risk patients, over and above the backdrop of self management education and a good clinical service, is costly and ineffective. Similar results have been found in telemonitoring trials with high level usual care.[7-10] The alert system creates a high workload, is expensive, and may result in a large number of false positive alerts and overtreatment. These were identified as concerns in the piloting phase,[12] and were borne out by the trial.

The most effective components of self management support services for COPD remain to be identified. Perhaps we should be putting more emphasis on a more "upstream" approach to prevent exacerbations. These are usually caused by viruses, and interventions that incorporate simple public health approaches for infection control may be worth pursuing.

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RESEARCH, p 12

- News: US moves to ban trans fats (*BMJ* 2013;347:f6749)
- News: Food firms' pledge on saturated fat is "thinnest of thin interventions" (*BMJ* 2013;347:f6523)
- Observations: Saturated fat is not the major issue (*BMJ* 2013;347:f6340)
- Research: The effect of rising food prices on food consumption (*BMJ* 2013;346:f3703)

India has a problem with palm oil

A substantial tax could be part of the solution

Bhavani Shankar professor of food, agriculture, and health, Leverhulme Centre for Integrative Research in Agriculture and Health and School of Oriental and African Studies, London WC1H 0PD, UK b.shankar@soas.ac.uk
Corinna Hawkes head of policy and public affairs, World Cancer Research Fund International, London WC1B 3HH, UK

The taxation of foods to improve health is an active area for research and policy making around the world. The literature generally shows that large food taxes can influence consumption and health.[1] However, the low levels of taxes typically considered, along with the weak responsiveness of consumption to price changes, mean that studies often report only a small impact on health.[2] The distributional consequences of "fat" taxes have also been debated—such taxes impose greater economic burden on lower income groups, although health benefits are also higher for these groups.[1 2]

In the linked article (p 13), Basu and colleagues simulate the effects that a 20% tax on palm oil would have on serum cholesterol and mortality from coronary heart disease and cerebrovascular disease in India.[3] The modelling approach combines an economic model of household consumption with a health microsimulation model that translates changes in oil consumption arising from the tax into changes in mortality from myocardial infarction and stroke.

This study is a valuable contribution to knowledge for several reasons. Firstly, it is one of the few studies on fiscal food policy for health to be conducted in a low to middle income country, where consumers are likely to be more responsive to tax induced price changes than in high income countries.[4] Secondly, the outcome measures considered go beyond consumption or nutritional outcomes to health outcomes. Thirdly, although palm oil is understudied, it is now the world's most consumed oil and of great importance to the health, environment, and economies of Asia.[5]

Basu and colleagues also calculated a simple measure of the potential adverse effects of the tax on food security by calculating the shift in the distribution of energy intake at the population level and report a small increase in food insecurity. Future research in this area might usefully consider this important dimension in more detail—for example, by investigating economic burdens and health benefits by income level.

If palm oil were taxed, consumers would probably reduce their consumption. The question is what would they replace it with? A merit of this study is that it incorporates substitutions between oils into the model, a clear improvement on many studies that ignore substitution,[1] or that restrict themselves to studying broad policy measures (such as a tax on all oils) because of data shortcomings or for analytical convenience.[6] Substitution between oils with varying levels of saturated and polyunsaturated fats has an important bearing on health outcomes.

Although the authors estimate a modest impact of a palm oil tax on hyperlipidaemia and resultant mortality, their estimate is limited to direct (cooking) consumption of palm oil by households. As the authors acknowledge, the food processing industry is also an important consumer of palm oil, so confining their analyses to household consumption may have underestimated the overall effect of taxation. Palm oil is popular with manufacturers of processed foods because it is saturated, and foods processed with saturated fats have longer shelf lives.[7] Manufacturers will continue to use palm oil unless incentives change.[8] A tax on palm oil could alter incentives not just for householders, but also for the (rapidly growing) food processing sector in India,[9] potentially resulting in further benefits to population health.

Although palm oil is understudied, it is now the world's most consumed oil

Policies to reduce the consumption of palm oil, including taxation, must take into account the possibility that the food processing industry would simply switch to another source of unhealthy fats—trans fats. Trans fats are also attractive to manufacturers of processed foods. In India, though, palm oil is also connected to trans fats in another form—"vanaspati." Vanaspati is a vegetable ghee used by households that is partially hydrogenated, with as much as 50% trans fat content.[10] Whereas vanaspati typically consisted of other oils in the past, palm oil and its fractions are now reported to form a major proportion of oils used in its manufacture.[10] A tax on palm oil could potentially reduce the incentive for its use in vanaspati, but additional actions would also be needed to limit trans fats in the Indian food supply, as a regulation proposed by the Food Safety and Standards Authority of

India would do. A leading reason for the success of palm oil lies in its relatively low price and production costs. This is what has enabled it to make such inroads into markets that were traditionally dominated by other oils, in India and around the world. When palm oil began to pour into India after it opened up its import markets in the mid 1990s, the government may have been wise to consider greater policy support for oils with healthier fatty acid profiles. The same could be said of the huge investments made into palm oil by international financial institutions.[11]

Furthermore, the low costs of producing oil palm, the source of palm oil, have been enabled in part by costs to the environment. Between 1990 and 2005, 2.7-4 million hectares of forest were lost to oil palm in Indonesia and Malaysia alone.[12] To the extent that a palm oil tax on a major importer like India would act as a brake on oil palm expansion elsewhere, the resultant lowering of greenhouse gas emissions would potentially offer a range of benefits, including to health. However, the production and trade of palm oil also brings important economic benefits. A research agenda—with policy development at its heart—that will link the economic, health, and environmental dimensions of the palm oil problem is urgently needed. Basu and colleagues' article is an important step in that direction.

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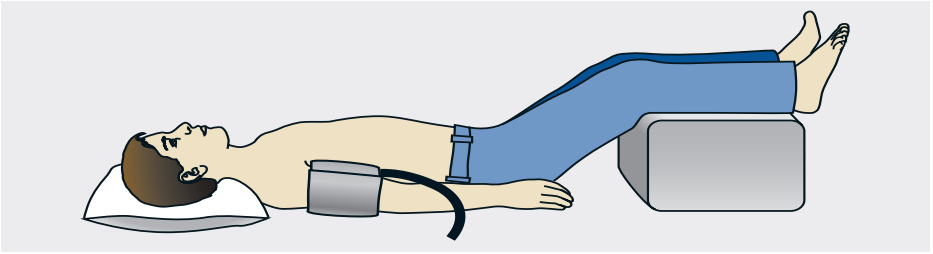
RESEARCH, p 13

There is a clear need to improve postmarketing surveillance of α blockers considered to have minimal risks of orthostatic hypotension

Severe hypotension associated with α blocker tamsulosin

Selective action does not guarantee safety

Jorge Ramirez professor of pharmacology, Universidad Icesi, Cali, Colombia Cali 00000, Colombia
jorge.h.ramirez00@gmail.com



Benign prostatic hyperplasia is the main cause of lower urinary tract symptoms in men—voiding, storage, or post-micturition symptoms are common to several genitourinary and neurological diseases. Men with these symptoms experience decreased quality of life, depression, and loss of productivity. The prevalence of these symptoms varies from 15% to 60% of men over 40 years of age.[1]

Worldwide, population ageing is contributing to the increasing burden of benign prostatic hyperplasia. This is accompanied by increasing healthcare costs owing to the growing list of treatment options. The study by Bird and colleagues (p 14) evaluates the safety of one such treatment option—tamsulosin, a selective α adrenergic receptor antagonist (α blocker). The authors report a significant association between starting or restarting tamsulosin and hypotension severe enough to require admission to hospital.[2]

Tamsulosin was introduced in 1996 and marketed as a major innovation among α blockers because it was associated with a lower frequency of orthostatic hypotension than other drugs in this class. Tamsulosin now dominates the global drugs market for the treatment of benign prostatic hyperplasia and is the most commonly prescribed treatment for lower urinary tract symptoms worldwide. It is available in many different doses and formulations and is manufactured by a range of drug companies.

Tamsulosin is available without prescription (over the counter) in the United Kingdom, thanks to its supposedly benign therapeutic profile. Selective binding of tamsulosin to prostatic receptor α1A/D instead of vascular receptor α1B receptors explains its lower rate of postural hypotension compared with other agents.[3] Concentrations of tamsulosin are higher in the prostate than the blood of men with benign prostatic hypertrophy. Importantly, though, we have no comparable information about the relative concentration of other α blockers in the prostate and blood to support claims of superior tissue selectivity for tamsulosin.[4]

Evidence from systematic reviews suggests that tamsulosin is moderately effective, at best, for men with lower urinary tract symptoms.[5] Moreover, α blockers do not improve clinical outcomes of benign prostatic hypertrophy or slow down growth of the prostate. There is no clear evidence that any one α blocker is clinically better than another. Despite the availability of new treatment options for relieving lower urinary tract symptoms, the rate of presentations to emergency departments for urological diseases has remained stable, whereas costs associated with hospital admission have increased by 40%, according to one estimate from the United States.[6]

Concerns about α blockers originally emerged from hypertension trials such as ALLHAT, which was published in 2000 and reported that doxazosin was associated with inferior efficacy and worse side effects than the diuretic chlortalidone.[7] The resulting shift away from using α blockers to treat hypertension, and the belief that their side effects were caused by their non-selective effects, triggered further development and marketing of so called uroselective options. During the past decade, the uroselective α blockers, alfuzosin and silodosin, have been approved by regulatory agencies in the United States, Europe, and many other countries around the world.

The hypotensive effect of α blockers may be exacerbated by cotreatment with other vasodilating drugs including phosphodiesterase type-5 inhibitors, although evidence about clinically important interactions is conflicting. Recently, tadalafil was approved by the Food and Drug Administration (2011), European Medicines Agency (2012), and other national regulators for the treatment of men with benign prostatic hypertrophy. Fixed combinations of α blockers and a phosphodiesterase type-5 inhibitor are already being developed by some drug companies. As Bird and colleagues have shown, severe hypotension is a problem even for drugs considered to be low risk.

There is a clear need to improve postmarketing surveillance of α blockers considered to have minimal risks of orthostatic hypotension. We also need much better evidence to determine the cardiovascular safety of α blockers combined with phosphodiesterase type-5 inhibitors.

The assumption that selective agents such as tamsulosin could be combined safely with a phosphodiesterase type-5 inhibitor is based on small clinical trials with limited follow-up.[8] Publication bias may also be a problem. There are registered studies evaluating the combination of 5PDI and α blockers that have never been published, including two completed in 2009 that evaluated the combination of α blockers with tadalafil (NCT00848081) and vardenafil (NCT01207947).

Randomised trials have many strengths, but they are not always the best way to detect adverse drug reactions.[9] Active pharmacovigilance studies (such as cohort studies) will provide a better understanding of the cardiovascular side effects of commercially available and widely used α blockers, including tamsulosin. These studies could also explore aspects of treatment not reported by Bird and colleagues, such as drug interactions (CYP3A4 inhibitors and phosphodiesterase type-5 inhibitors), as well as the effect of different doses and different formulations of tamsulosin (such as oral controlled absorption system or modified release). In the meantime, Bird and colleagues' study should be carefully reviewed by national regulatory agencies and healthcare policy makers.

Doctors have a tendency to embrace new therapeutic options with enthusiasm, but we often forget that the history of drug development repeats itself, telling us that "new generations" of existing drugs are rarely truly novel, no matter how remarkable their pharmacokinetic and pharmacodynamic properties seem to be.

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RESEARCH, p 14