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Dietary iron and blood pressure

Iron intake may affect blood pressure, but further confirmation is needed

ROBERT WHITE/CORBIS

RESEARCH, p 15

Saverio Stranges associate clinical professor of cardiovascular epidemiology, Clinical Sciences Research Institute, University of Warwick Medical School, Coventry CV2 2DX
S.Stranges@warwick.ac.uk

Eliseo Guallar associate professor, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205, USA

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Nutritional and lifestyle factors are key determinants of blood pressure across populations, and lifestyle modifications—including weight reduction if overweight or obese, reduced dietary sodium intake, increased dietary potassium intake, moderation of alcohol consumption, adoption of the DASH (dietary approaches to stop hypertension) diet, and regular aerobic exercise—are effective at reducing blood pressure.¹

In the linked study (doi: 10.1136/bmj.a258), Tzoulaki and colleagues assess the association between iron and red meat intake and blood pressure using data from the international collaborative study of macro-/micronutrients and blood pressure (INTERMAP), a large cross sectional study of the nutritional determinants of blood pressure across 17 population samples from Japan, China, the United Kingdom, and the United States.² The authors found significant inverse associations between intake of total iron and non-haem iron and systolic blood pressure. Conversely, intake of red meat was significantly associated with increased systolic blood pressure, but the association between intake of haem iron and blood pressure was not significant.

Substantial experimental evidence has linked iron overload with accelerated atherosclerosis, and diets deficient in iron have been linked with reduced atherosclerosis,³ but whether there is a link between iron and coronary heart disease is still uncertain. Firstly, meta-analyses of the association of biomarkers of iron metabolism—such as ferritin and transferrin saturation—with coronary risk have mostly found no associations.⁴ Secondly, a large randomised controlled trial in which phlebotomy was used to reduce iron stores in patients with symptomatic peripheral arterial disease found that iron reduction had no effect on cardiovascular end points,⁵ although iron reduction may have been beneficial at younger ages. Thirdly, mutations in the gene encoding the hereditary haemochromatosis protein (HFE) do not seem to be associated with the risk of heart disease,⁶ possibly as a result of lower concentrations of low density lipoprotein cholesterol in people with HFE mutations.⁷ Lastly, prospective studies have also failed to show a clear association between iron intake and the development of coronary heart disease.⁸ Interestingly, the pattern seen in the health professionals' follow-up study was similar to the pattern seen in INTERMAP: an inverse association for total iron and positive association for haem iron in relation to the risk of coronary heart disease.⁸

The study by Tzoulaki and colleagues provides new data that underline the complexity of the association

between iron and heart disease.² The authors studied intake of haem and non-haem iron separately, because these two types of iron have different sources and pharmacokinetics, which affects their absorption and bioavailability. Non-haem iron comes mostly from vegetable foods, whereas haem iron is derived mostly from animal sources, mainly meat and seafood. Furthermore, healthy people adapt to reduce the absorption of non-haem iron but not haem iron in response to iron supplementation.⁹

The mechanistic explanation for an inverse association between non-haem iron and blood pressure, however, is unclear. Iron is a highly reactive metal that is easily oxidised and reduced and which may participate in the generation of powerful oxidant species. Indeed, iron induced oxidative stress has been hypothesised as a primary mechanism in diabetes associated with iron overload.¹⁰ Even moderately raised iron stores and plasma ferritin concentrations, below those seen in haemochromatosis, might be associated with insulin resistance, diabetes, and the metabolic syndrome.¹¹ Because increased oxidative stress might play a role in the pathogenesis of hypertension, mechanistic studies should clarify why non-haem iron may be associated with lower blood pressure, or why the effects of haem and non-haem iron on blood pressure are different.

Even though INTERMAP is a high quality study, it highlights the difficulty in establishing a causal association between a nutrient and a physiological outcome on the basis of a single observational study. The cross sectional nature of INTERMAP precludes the possibility of sorting out the temporality of the observed associations. Perhaps more importantly, confounding effects by additional dietary and lifestyle variables are likely, because iron intake is correlated with other nutrients, foods, lifestyle characteristics, and socioeconomic factors.

The observed effects could be the result of different dietary patterns—people who eat lots of red meat have a higher intake of haem iron than those with a more vegetarian diet, who take in more non-haem iron. Misclassification of iron intake from dietary recall is substantial and may have biased the observed associations between iron and blood pressure. Because nutrients and foods are highly correlated and the errors in estimating nutrient intakes are also correlated, measurement error may bias the observed associations away from or towards the null. In addition, confidence intervals that do not take measurement error into account probably under-represent the statistical uncertainty of the data.¹²

Prospective studies, randomised evidence, and

mechanistic studies in experimental models are needed to establish whether dietary iron has any effect on blood pressure levels.

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Co-trimoxazole for HIV infected adults

Reduces mortality even where bacterial resistance may be high

HOWARD BURDITT/FMS/REUTERS

In their linked study, Nunn and colleagues report the results of a placebo controlled trial of co-trimoxazole prophylaxis in HIV positive Zambian adults being treated for tuberculosis. They found that co-trimoxazole significantly reduced mortality (hazard ratio 0.79, 95% confidence interval 0.63 to 0.99), and they conclude that the findings strengthen the evidence base for the World Health Organization and the Joint United Nations Programme on HIV/AIDS (UNAIDS) guidelines issued in 2000.¹ Despite the now overwhelming body of evidence the findings have been only partially translated into practice.²⁻⁹

Prophylaxis with co-trimoxazole was used in industrialised countries two decades before it appeared in Africa. In the early 1980s, co-trimoxazole was already being used to prevent bacterial infections in people with granulocytopenia who were HIV negative.

Why were American and European recommendations not transposed directly to Africa? Firstly, evidence indicated that pneumocystosis was rare in African adults. In contrast, HIV related bacterial diseases often caused death.¹⁰ Prophylaxis with co-trimoxazole, which was “primarily antiparasitic” in industrialised countries, therefore needed to become “predominantly antibacterial” in Africa. The implications of this functional shift in policy—especially the question of when to start prophylaxis—were not entirely clear. Secondly, some adults with HIV in industrialised countries were intolerant of co-trimoxazole and had to interrupt treatment. In resource limited settings poor tolerance combined with more limited access to care might alter the risk to benefit ratio of the intervention. Finally, in Africa, HIV is often first diagnosed when patients start treatment for tuberculosis, and tuberculosis is the leading cause of death in patients with HIV.¹¹ This explains why some studies specifically targeted such patients.

Two placebo controlled trials of co-trimoxazole in Côte d'Ivoire were published in 1999. One was carried out in adults with HIV being treated for tuberculosis,

with mortality as the primary outcome. It showed that co-trimoxazole reduced mortality by 46% (hazard ratio 0.54, 95% confidence interval 0.38 to 0.77).⁹ The other study was in adults with HIV at WHO stage 2 or 3, with severe morbidity as the primary outcome. It showed that co-trimoxazole reduced severe morbidity by 47% (hazard ratio 0.57, 95% confidence interval 0.43 to 0.75).² In both trials, co-trimoxazole was better tolerated than expected. In subgroup analyses both trials showed that the efficacy of co-trimoxazole was not restricted to patients with fewer than 200 CD4 cells $\times 10^6/l$. Co-trimoxazole prevented malaria, invasive bacterial diseases, and isosporiasis. The immediate consequences of this evidence seemed logical. Firstly, two other African placebo controlled trials were stopped prematurely. Secondly, WHO/UNAIDS experts recommended that co-trimoxazole be part of the minimal package of care for African adults with fewer than 500 CD4 cells $\times 10^6/l$.

Since 2000, policies on co-trimoxazole have varied widely across the continent, ranging from no prophylaxis to prophylaxis started at different CD4 thresholds. The main argument for deciding not to follow standardised policies stemmed from the question of whether co-trimoxazole will work in countries where bacterial resistance to this drug may be higher than in Côte d'Ivoire. Between 2000 and 2008, six non-randomised studies tackled this question. All found that the answer was “yes.”³⁻⁸ Further confirmation comes from Nunn and colleagues' randomised trial. Hopefully, their results will convince the very last sceptic.

Bacterial diseases such as tuberculosis are curable in settings with high standards of care but cause death when access to diagnosis and treatment is limited.¹⁰⁻¹² This is why it is preferable to prevent these diseases. In sub-Saharan Africa, prophylaxis with co-trimoxazole and isoniazid are effective and these drugs should be prescribed. Trials are needed to assess their main alternative—starting antiretroviral therapy earlier.

RESEARCH, p 220

Xavier Anglaret senior researcher, INSERM, U593, Université Bordeaux 2, 33076 Bordeaux, France
Xavier.Anglaret@isped.u-bordeaux2.fr

Serge Eholie professor of infectious diseases, Service des Maladies Infectieuses et Tropicales, CHU de Treichville, Abidjan, Côte d'Ivoire

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A strategy for end of life care in the UK

We need to overcome taboos about death and communicate better

Julia Riley head of department, palliative medicine, Royal Marsden Hospital, London SW3 6JJ
Julia.Riley@rmh.nhs.uk

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Around 500 000 people die in England each year, and this number is predicted to rise to around 530 000 by 2030. Death affects every person, family, and community, and every culture and creed has its own way of dealing with it. We should all have an interest in good end of life care, yet death is not culturally acceptable, and it is a taboo subject to the public and the medical profession. In a recent BBC survey, only 34% of the general public reported that they had discussed their wishes for how they would like to die. Many healthcare professionals consider it a failure when patients die. In April 2008, the Heath Commission reported that no less than 54% of complaints related in some way to end of life care.

Last week the Department of Health published its strategy for dealing with end of life care in the United Kingdom.¹ Producing such a strategy is challenging because it incorporates health care, social care, spiritual care, and all possible sensitivities, as well as homeless people, prisoners, and mentally disabled people. More than 300 stakeholders were consulted. We need to consider how end of life care should change, how the strategy will facilitate this, and how we can measure success.

Most people say they would prefer to die at home, yet the reality is that most deaths (58%) occur in NHS hospitals, with only 18% occurring at home, 17% in care homes, 4% in hospices, and 3% elsewhere.¹ Where patients die is influenced by many factors.² The complexities of planning end of life care services are enormous. It is difficult to define exactly when end of life care starts and even more so to predict prognosis accurately.^{3 4}

The strategy outlines a six step end of life care pathway, which begins with honest communication between clinician, patient, and carer, and the identification of a trigger for discussion. Three themes underlie the six steps and continue throughout the pathway—support for carers and families, information, and spiritual services. However, the pathway is silent on the subject of psychological support, which is surely

a key factor throughout the journey.

The report describes many examples of good practice and suggestions of care, but data to support the recommendations are limited, and at present there are no minimum standards.⁵ It does acknowledge the lack of good evidence and recommends that clinicians start pooling data, auditing practice, and developing metrics. It is only then that research will be able to evaluate the effects of new models on quality of care.

Assessments of the economics of care packages must include measures of quality of life, family satisfaction, and burden on the carer. Medical professionals like to think that they give patients control, but this impression is countered by evidence that patients do not die where they would prefer to.¹ We must be able to test whether or not strategies are successful by including metrics, such as preferred place of care and preferred place of death, into patients' recorded outcome measures. When these metrics have been determined they should also be made available to the palliative care team (perhaps on "personal dashboards," which show in real time what is happening in terms of performance, as advocated by Professor Sir Bruce Keogh, NHS medical director). The natural competitiveness of clinicians might encourage them to improve their performance if the metrics show that their peers are doing better than they are.

High quality communication should be the essence of delivering the service, with the patient's wishes and care plan available at every contact with the service. Whenever an intervention of any sort occurs in primary care, secondary care, community services, or social services the patient's exact wishes must be known and complied with. The new strategy could make this happen by providing a contemporaneous document, and it is a challenge to the National Program for IT to show how such pathways can be enabled by electronically sharable documentation and plans.

Communication and training in symptom control

must be part of the core medical curriculum because the specialist palliative care workforce is relatively small.⁶ Almost all healthcare professionals will at some time care for dying patients, and they should have the skills to do it well.

The main aims of this end of life care strategy are the delivery of high quality care, a change in culture, and better communication, and this is reflected in the proposed division of funds. A central Department of Health fund will support the necessary change in culture, linking public opinion and professional involvement. The government is committed to spending an additional £286m (€360m; \$570m) from 2009 to 2011, and it is refreshing to note that most of the funding will go to primary care trusts, making real the policy of devolution of responsibility and resources to the front line. Trusts will be key players in devising and implementing new ways of working.

Niall Dickson, chief executive of the Kings Fund, said of Lord Darzi's reforms that "real cultural change will be needed in the health service if the vision is to be translated into a reality."⁷ This applies in particular to this end of life care strategy. Dying has to become part of living, and we need to talk about it, plan for it, and encompass it.

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Consent for biobanking

Lack of dissent when opting in doesn't necessarily support "opt out"

RESEARCH, p 224

Graeme Laurie professor of medical jurisprudence, School of Law, University of Edinburgh, Edinburgh EH8 9YL
Graeme.Laurie@ed.ac.uk
 Competing interests: None declared.

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In the linked study, Johnsson and colleagues report levels of dissent in Swedish patients who are asked about storage and future research use of samples collected during health care.¹ Only 0.14% of patients dissented to either storage or use of their samples, and 0.063% confirmed their decision by completing a dissent form.

The authors conclude that their survey provides evidence of high levels of trust in the Swedish system, and although this might not translate to other countries or contexts, it may support a move to opt-out systems of regulatory governance. Although the study concerns samples rather than data derived from them, the research value of samples lies in the generalisable data that they can generate, so questions about control of information and access to it are crucial. The suggestion that lack of dissent in an explicit consent system (opt in) may support a move to presumed consent (opt out) requires close scrutiny.

We need to decide what counts as evidence of support for biobanking practices, and more fundamentally, what counts as support for different regulatory mechanisms surrounding those practices. Central to answering these questions is the role and importance we give to consent as the legitimising factor in research and the handling of patient samples and records.

Respect for individual autonomy has become increasingly emphasised in recent years,² but it is often reduced to a crude imperative to obtain informed consent, and bears little relation to robust philosophical accounts of autonomy,³ which question whether fully informed consent and patient empowerment through consent processes are achievable, and instead suggest a more modest role in protecting patients against deception or coercion. Moreover, over-reliance on a need for consent can thwart other valuable social ends, such as scientifically robust medical research.

The obsession with the importance of consent, or "fetishisation" of consent, is seen across the entire range of biomedical activities. The Human Tissue Act 2004 is replete with references to the need for "appropriate consent" without defining the term. In the context of secondary uses of data the mantra of "consent or anonymise" guides the decisions of bodies such as the Patient Information Advisory Group in authorising research that uses patients' data. Anonymising samples also avoids the need for consent for research samples in England and Wales, but only with appropriate ethical approval. The Human Tissue Authority recommends that "obtaining consent is preferable to developing complex systems for keeping samples unlinked."⁴

The obsession with consent has been criticised in the context of using patient data for research because it is seen as an unduly restrictive means of governing research—consent is not always practicable or possible to obtain. Furthermore, the law does not strictly require explicit consent, and the consent or anonymisation rule also has limits because it can undermine or even block valuable research.⁵

Interestingly, legislation in Western Australia authorises the use of health data for research without the need for consent. Moreover, people cannot opt out because, as the guidance makes clear, "all Western Australians benefit from reliable information about health."⁶ In Europe, despite the rigours of the Data Protection Directive, official opinion says that electronic health record systems that include provision for research—which are justified by substantial public interest—could feasibly be set up, as long as specific and suitable safeguards are in place, such as opt-out provision.⁷ It is possible, therefore, to envisage and implement systems of health related research that do not require explicit consent.

The matter of public support or approval of such

approaches is another matter. Johnsson and colleagues take as their starting premise that an option of dissent might undermine research and that this threat might be more likely if patients' trust is eroding. They conclude that their results suggest that no immediate crisis of trust and so no immediate threat to research exists, at least in Sweden. It is not immediately obvious, however, why their results support a move to implied consent, or why that system would be better at tackling concerns—among the research community—that biobank research might be under threat.

If anything, the results of this study suggest that the current system works to promote respect for research and patients. The authors lament the high costs and complex administration of an opt-in system “to support a small minority of patients” who would say no. However, they may be overlooking the costs of establishing a defensible opt-out system that gives patients adequate information about who might have access to their samples or information, and for what purposes.⁷ The need for an evidence base to support opt-out systems should not be underestimated. Although the Icelandic health sector database had widespread public support,⁸ the opt-out system was not accompanied by robust public education campaigns or public engagement exercises and caused considerable ethical controversy as a result.⁹

The position in the United Kingdom on evidence of support for opt-in or opt-out systems is fragmented. The Organ Donation Taskforce is currently investigating the viability of an opt-out system for transplants.¹⁰ In contrast, the recent independent evaluation of the Summary Care Record Early Adopter Programme has recommended an urgent review of the current implied consent (opt-out) model, arguing that—for England at least—evidence exists of “widespread desire from patients and staff” for a simpler model of approval that requires explicit consent to view records.¹¹ The tentative suggestion is that this bet-

ter reflects where patients put their trust—in people and not processes. The system in Scotland requires implied consent to create an “emergency care summary”—an electronic record of basic patient information available to all NHS Scotland staff caring for a patient when the general practitioner surgery is closed—with explicit consent to view on each occasion; reports of dissent have been as low as 0.02% for this system.¹¹

What is missing from much of the evidence base to date in the UK, Sweden, and elsewhere is a better understanding of what patients and the public understand about samples, records, and research; how well informed they are; and whether low opt-out rates truly reflect well placed trust or simply poorly informed apathy. In particular, we should be cautious about concluding that low rates of dissent in an opt-in system provide evidence of support for an opt-out system.

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Tackling knife violence

Emergency departments should contribute to local crime reduction partnerships

Jonathan Shepherd professor of oral and maxillofacial surgery and director, Violence Research Group, Cardiff University, Cardiff CF14 4XY

Iain Brennan research assistant, Violence Research Group, Cardiff University, Cardiff CF14 4XY

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A spate of knife killings in the United Kingdom, largely of young Londoners, has prompted outrage in the media, fear on the part of citizens, and new policy proposals from government. According to the authoritative British crime survey, weapons were used in around a quarter of violent incidents in England and Wales in 2006-7, although the survey does not take account of crime affecting people under 16 years.¹ According to this source, the annual prevalence of knife use has remained constant at around 7% of all violent incidents since 2000. Hospital episode statistics show that rates of hospital admission in England after violence of all types increased (from 82.7/100 000 population in 2000-1 to 114.4/100 000 in 2006-7) at almost exactly the same rate as admissions after knife violence (from 8.5/100 000 to 11.3/100 000). In con-

trast, rates of treatment in emergency departments after violence of all types decreased from about 850 to 620 per 100 000 over the same time²; no national emergency department data are available on knife violence specifically. In summary, since 2000, violence in England and Wales has become less frequent, but injuries may have become more serious, which could explain the increase in hospital admissions. However, this increase could also reflect changes in admission policy, such as efforts to reduce emergency department trolley waits.

Proportions of knife violence in the United States (6.3% of all 2006 violence identified in the US national crime victimisation survey) are remarkably similar to those in the UK.³ Elsewhere, the international crime victimisation survey (which brings

together crime survey data from 28 countries) indicates that rates of knife violence are highest in Spain and Portugal and lowest in Scandinavian countries and Greece.⁴

People carry weapons for four main reasons—to increase their capacity to cause harm,⁵ because of fear of violence,⁶ to facilitate robbery,⁵ and to demonstrate “machismo.”⁷ The availability of weapons and the act of carrying them also determine their use. For example, the availability of handguns is a major determinant of deaths from firearms.⁸ As far as criminal justice interventions are concerned, increasing the perceived likelihood of being caught is a more effective deterrent than severity of sentence.⁸ Police interventions that target violence “hotspots” are also effective.⁹ In the absence of objective evaluations of interventions designed to reduce knife crime specifically, rational prevention policy should be based on these findings.

Restorative justice—where offenders are confronted with the consequences of their actions in conferences that include community representatives, the police, and their victims and which result in a heartfelt apology—reduces repeat violence.¹⁰ Fear of violence is known to be increased by evidence of criminal damage, litter, and graffiti¹¹—in effect, a disfigured environment sends messages that personal disfigurement may be next. Environmental interventions are therefore likely to reduce fear. Because the motivation for most robbery is related to drugs, tackling drug use and markets will probably reduce the carrying of weapons.

Demonstrations of machismo are used by assailants to dissuade victims from reporting violence to the police. Many violent incidents that result in medical treatment are not reported to the police because patients are afraid of reprisals, they are unable to identify assailants, or they are unwilling to have their own conduct scrutinised. Emergency departments can help by collecting anonymised data on the locations and times that violent events occur and the types of weapons used, and by sharing these data with crime reduction agencies. Clearly, unless violence hotspots are identified, they cannot be targeted. It is not safe to assume that the most serious violence, including knife and gun violence, will have been reported.¹²

UK legislation on violent crime in the past 10 years has done much to promote data sharing, including the introduction of more than 350 statutory Crime Reduction Partnerships (Community Safety Partnerships in Wales and Scotland) to which the NHS, local authorities, and the police must contribute. Evaluations provide evidence that this integrated approach significantly reduces violence compared with the police and local authorities working alone.¹³ The unique data derived from emergency departments and the influence of emergency department consultants working in these partnerships have emerged as distinctive and effective NHS contributions.

If the patient or other people are at risk of further violence, the police should be contacted promptly and directly—with the consent of the patient if possible, but without this if necessary. Here, as with child protection, discretion is needed, but some assessment of risk of further harm is necessary in all health services in which adults and children who are injured in violence are treated.

Measures that decrease the availability of knives, including criminalisation of knife carrying, are also rational. Metal detector wands and arches at strategic street and public transport locations may be effective.¹⁴ More strategically, violence is now recognised by the World Health Organization as a global public health problem and a barrier to international development.¹⁵

The lack of evidence of effectiveness of specific measures to tackle knife crime exemplifies that, compared with medical science, the evidence base for the crime sciences is in its infancy. Whereas medicine is underpinned by rigorous applied research integrated with practitioner training in university schools, police, probation, and prison services lack these foundations. In the 19th century, Sir William Osler successfully demanded an “invasion of hospitals” by universities, paving the way for the exponential increase in clinical experiments and much more effective health care in the next century. It is high time our best universities invaded the criminal justice system.

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