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Pandemic obesity in Europe

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Risk assessment after acute coronary syndrome

Lots of potential but will it end up being yet another risk score?

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A range of presentations of ischaemia is seen in acute coronary syndromes, from unstable angina at one end of the risk spectrum to myocardial infarction (with or without ST elevation) at the other. In all these disorders the risk of death is highest before admission to hospital, with mortality rates of up to 20%. Risk remains high after admission to hospital, and although mortality rates have fallen greatly in recent years,¹ up to 7% of patients die before discharge, and risk continues to be high for six months after the ischaemic event.² Minimising the risk of complications relies on identifying and treating patients at higher risk early on. In this week's *BMJ*, a multinational study by Fox and colleagues assesses the effectiveness of a risk prediction tool in estimating cumulative six month risk of death or myocardial infarction in people presenting with acute coronary syndrome.³

On presentation to hospital, patients are often triaged on the basis of concentrations of biomarkers and ST segment changes into three groups—those who need immediate reperfusion therapy (ST elevation myocardial infarction), early angiography with a view to revascularisation (non-ST elevation myocardial infarction), or medical treatment only without routine catheter laboratory intervention (troponin negative unstable angina). This triage system also provides a crude basis for risk stratification as patients with myocardial infarction have a greater risk of death than those with unstable angina.⁴ However, risk stratification based simply on biomarkers and changes in electrocardiography fails to reflect the diversity of risk within these diagnostic subgroups. Many attempts have been made to refine the process of risk assessment further, but none of these newer tools has been adopted in clinical practice.

Will the global registry of acute coronary events (GRACE) scoring system described in this week's *BMJ* prove more useful in clinical practice?³ Fox and colleagues reassuringly confirm what doctors already recognise—high risk patients are elderly, have left ventricular failure, and have documented ST changes. These variables are components of other scoring systems, however, and the value added by each of the additional clinical factors incorporated into the GRACE score is not known. In other words, how many patients who would have been identified as low risk could theoretically benefit from treatment and how many patients with an inflated risk could be spared potentially harmful treatment if the GRACE scoring system were implemented? The stated goal of the new score is to provide a simple but robust basis for guiding

care in hospital and after discharge for patients with acute coronary syndrome but stops short of suggesting how. Doctors are left to ponder at what point in the scoring system the large number of patients with acute coronary syndrome at intermediate risk justify a different management approach than is used for patients at the extremes.

Another potential weakness relates to the cohort of patients recruited. The score was developed and validated in selected cohorts of patients from voluntarily participating hospitals, the response rates are unclear, and patient recruitment was not explicitly consecutive in all cases—so was not strictly random. This may explain why hospital mortality rates seem lower than would be expected from comparable UK data.⁵ Despite this, the score appears more representative of patients across the spectrum of acute coronary syndromes than those developed previously.^{6,7}

Other factors independent of the risk score determine which treatment patients will receive. Interventions such as secondary prevention drugs and lifestyle advice are (or should be) given to all patients before discharge from hospital regardless of risk—a management policy that will be unaffected by risk score. Timely revascularisation may reduce risk in selected patients with acute coronary syndromes, yet patients at highest risk such as elderly patients⁸ and those with left ventricular failure are least likely to be referred. Indeed, such referral patterns in combination with angiographic findings often drive decisions on revascularisation in high risk patients,⁹ and provide a recipe for inequity that risk scores have the potential to remedy. If this treatment bias can be corrected by using the risk calculator of Fox and colleagues this might prove to be its greatest asset. If patients were treated according to their risk of events rather than referral patterns, older patients, for example (who benefit from coronary artery bypass grafting but are less likely to be referred for it) might get treated.

Fox and colleagues conclude that risk prediction tools may potentially guide therapeutic interventions in the future. This highlights how useful risk scores could be in clinical practice; for example, in predicting long term outcomes and alternative endpoints to death, which occurs in a minority of patients after an acute coronary event. The authors stress that their score may not be appropriate for low risk patients with non-specific chest pain without acute coronary syndrome. This emphasises the need of accurate risk stratification upstream from tertiary care; that is, primary and

secondary care and interfaces such as rapid access chest pain clinics, where a surprising number of such patients develop cardiac endpoints.¹⁰ This forces the question of whether the Fox and colleagues' risk score really is so different from that proposed for patients with myocardial infarction in the late 1960s,¹¹ or whether we should take a closer look at why risk assessment in general is so difficult to adopt in clinical practice.

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Educational performance in twins

Is no different from that seen in singletons by adolescence

In this week's *BMJ*, Christensen and colleagues¹ investigate two questions that are of popular and medical-scientific interest. Firstly, do twins have lower intellectual skills and educational achievements than singletons and, secondly, is birth weight associated with intellectual and educational performance? The authors look at the second question in both twins and singletons. They also open up the question of the link between intelligence and education, because the main comparator studies used IQ-type outcomes rather than educational performance.^{2 3}

The study uses the Danish registration system linked with the Danish demographic database, the national hospital discharge register, the register of compulsory school completion assessments and test scores, and the Danish twin registry. They therefore had data on standard national educational outcomes, birth weights, and other demographic and parental variables for the entire relevant population of twins, and for a large representative sample of the comparable population of singletons.

Firstly, do twins have lower intellectual skills and educational achievements? Three recent studies of large samples of Scottish children born between 1921 and the 1950s strongly suggest they do. The Scottish mental surveys of 1932 and 1947 tested the IQ of most 11 year old Scottish children born in 1921 and 1936, respectively. In both surveys, twins scored about 5 IQ points (one third of a standard deviation) lower than singletons.² Father's social class, overcrowding in the home, height during childhood, school attendance, and number of people in the family did not account for the twin-singleton difference. The third study, in children from Aberdeen in the 1950s, found a similar twin-singleton difference in IQ test scores at ages 7 and

9.³ It had the added benefit of comparing twins and singletons in the same families. The authors of that study found partial attenuation of the effect after adjusting for birth weight and gestational age.

However, Christensen and colleagues found similar test scores for twins and singletons. One possible reason for their findings, apart from possible differences between countries and populations studied, is the age at testing (at least five years later in the present study). This is supported by a Dutch study of adult twins, which found no significant difference in IQ between singletons and twins from the same families.⁴ It is therefore possible that differences in ability or educational performance (or both) exist between twins and singletons as late as 11 years, but that they disappear by 16.

The comparison of Christensen and colleagues' findings with other recent large twin studies relies on there being a strong association between intelligence and educational performance. A large longitudinal representative study of more than 70 000 English schoolchildren supports this link.⁵ General intelligence scores at age 11 years, derived from a battery of 10 separate cognitive tests, were highly correlated ($r > 0.8$) with general performance in the GCSE examinations at age 16. Interestingly, despite no differences in general intelligence being seen between boys and girls at age 11, girls performed considerably better in GCSEs at 16.

Secondly, is birth weight related to intellectual skills and achievements? Certainly, infants born well below the normal range of birth weights have some disadvantage.⁶ Few studies have focused on the normal range of birth weights and term births, and the variability in the design of such studies does not allow a meta-analysis to be carried out. Overall, though, a

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narrative systematic review of such studies found a small positive association between birth weight and childhood (up to age 17) IQ that was not accounted for by parental social class.⁷

The study by Christensen and colleagues also finds a small effect of birth weight on educational performance. Even that small effect could be due to confounding, however. A recent study based on the US national longitudinal survey of youth 1979 found that the small significant association between birth weight and language and mathematical achievements in childhood and adolescence was largely accounted for by the mother's IQ score. This indicates that brighter mothers have brighter and heavier children.⁸ If we put this potential confounding factor aside though, educational attainments are almost identical for each centile of birth weight (not absolute weight) within the singleton and twin groups. Christensen and colleagues conclude that the relative position of twins within their own group with respect to birth weight is most important. Such an effect is not unique to twins versus singletons or to birth weight and educational performance. Consider a comparable situation. A meta-analysis found a moderate sized correlation between brain volume and IQ⁹; men have, on average, bigger brains than women, yet men and women differ little in mean general intelligence.¹⁰ Therefore, it is possible for birth weight and IQ to be related within both singletons and twins, and for twins to be on average lighter than singletons, and for twins and singletons not to differ in intellectual skills and achievements.

There remain unresolved issues about the possible effects of differences in geography, year of birth, and age. But the mechanisms by which these factors could eliminate twin-singleton differences is unclear. Consider year of birth, for example. Christensen and

colleagues suggest that better, more recent obstetric care might be responsible. But it is tenable that such differences in care might also assist the survival of more at-risk babies generally—twins as well as singletons. Therefore, it is not clear whether better obstetric care would reduce, increase, or not affect any prior twin-singleton difference in mental ability. Despite these issues, Christensen and colleagues' study is comprehensive and well executed enough to reverse a trend in our thinking—that twins perform less well than singletons.

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Pandemic obesity in Europe

A new charter from WHO promises concerted action to prevent and treat obesity

The threats to public health from widespread obesity are well known. So are the main solutions—we all need to move more and eat less. Evidence is still sparse, however, on the effectiveness, and, importantly, the cost effectiveness of large scale public health interventions to prevent and treat obesity. But a fifth of Europe's population is already obese, and obesity in adults accounts for up to 6% of direct health costs and more than 12% in indirect costs of shortened lives, reduced productivity, and lowered incomes.¹ Can Europe afford to wait for better evidence? The World Health Organization does not think so.

This month in Istanbul, WHO brought together from all corners of Europe ministers of health; ministers from other sectors such as education, sport, environment, transport, and agriculture; the food industry; public-private partners; and non-governmental organisations with the aim of taking real and immediate action on obesity. The meeting was more than a high level talking shop. The immediate and most obvious outcome was that all 53 states in the WHO European region adopted a new action plan into government policy. The

plan, the European Charter on Counteracting Obesity, sets out what the region's states could and should do to halt and eventually reverse the pandemic.²

The charter calls for preventive actions including promoting breastfeeding; cutting salt, sugar, and fat in foods; promoting physical activity and better nutrition in schools; and designing urban areas for people and bicycles rather than cars. This is familiar advice on what to do, but the charter goes further by suggesting how to do it. And, while the proposals do not comprise what a management consultant would call truly SMART objectives—specific, measurable, achievable, realistic, and time specific—they do spell out important priorities and mechanisms for action (see box on bmj.com). The WHO European regional office is following up the Istanbul conference with a detailed action plan and will report on progress across the region every three years from 2010.

How will WHO know if European member states are making progress and, importantly, if any fall in the

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prevalence and burden of obesity can be attributed to actions prompted by the charter? At present WHO cannot even reliably monitor Europe wide trends related to obesity, because national health surveillance systems do not routinely use internationally comparable measures. According to the charter, this evidence gap will soon be plugged through the development and widespread use of a set of core performance indicators.

Research on effectiveness of large scale public health programmes is much harder to do than surveillance, and cannot prove cause and effect. But this does not mean that epidemiological, time series, and cost-benefit studies should not be done, and the usual exhortation that more research is needed clearly holds true for tackling obesity. New and authoritative reviews on obesity from the US Institute of Medicine³ and WHO⁴ list important outstanding research questions, and next month's extensive guidance from the UK's National Institute for Health and Clinical Excellence (NICE) will give—along with guidelines for good practice—detailed recommendations on the aims and design of future research.⁵

Who will pay for research on what works in tackling obesity? The European Union's programme for health research from 2007-13 favours biotechnology studies over those on public health and health services,⁶ and industry has little incentive to fund such work. More-

over, the overall EU budget for health was virtually halved earlier this year. One participant at the Istanbul conference said that we will not beat obesity until we seduce people into living healthier lives. To make the new WHO charter achievable and realistic as well as specific and measurable, the first people to seduce are Europe's finance ministers.

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Opinion leader interventions in social networks

Can change HIV risk behaviour in high risk communities

Disadvantaged populations who have poor access to health care are particularly vulnerable to the effects of HIV and sexually transmitted diseases. They are less likely to be routinely tested for HIV and sexually transmitted diseases. If they test positive they are often unable to afford the required treatments. Efforts have been made to curtail the spread of HIV and sexually transmitted diseases in many populations. Interventions have evolved from traditional classroom-type presentations that focus on the individual to those that involve couples and aim to improve their communications. Other interventions have used street theatre and novellas broadcast on television or radio. Most of these interventions have had only modest effects on behavioural change.

A study in this week's *BMJ* by Kelly and colleagues reports the effects of a social network intervention designed to reduce risky behaviour that can lead to HIV and sexually transmitted diseases in a high risk population of Roma (Gypsy) men in Bulgaria.¹ In the intervention arm of the study, leaders of Roma men's social networks counselled their own network members about reducing the risk of HIV and sexually transmitted diseases. The study found that people receiving the intervention had lower rates of unprotected intercourse over 12 months and had higher scores on knowledge related to AIDS, attitudes, and motivations to change behaviour.

This study is important for several reasons. Firstly, by using social network nominations it is a more

sophisticated form of the peer opinion leader model used to great effect in many other studies.²⁻⁴ It also shows that opinion leaders should be identified by interviews with members of the social network rather than through observations by staff carrying out the programme. Such a social network method is a valid and reliable way of identifying opinion leaders and also provides a standardised protocol that can be replicated.²

Secondly, the study shows that even in marginalised communities, who may distrust government and other institutions, peer opinion leaders and programme staff can build trust through mutual understanding and can produce positive outcomes. If the approach works here, it is likely to be feasible in other places and with other populations.⁵

Thirdly, the study showed effects across a range of outcomes, from improving knowledge of HIV and sexually transmitted diseases and attitudes towards them to more objective outcomes like reducing the incidence of these diseases in the long term. Thus, the behavioural change is likely to be self sustaining and self propagating. Indeed, effects are likely to be an underestimate as people in the intervention group may have shared knowledge with people outside the group, thereby diluting the effect.

Although other opinion leader interventions have been effective in both clinical and community settings,^{4,6} this one may have been more effective because of the small size of the networks. Leaders were identified within small groups so the intervention was

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essentially a peer leader network intervention. So while the effectiveness of leaders may vary according to relationships within networks (tie strength, closeness, etc), in this study the social distance between leaders and group members was small. In other applications, it may be necessary to use network data and algorithms that are designed to minimise social distances between leaders and group members.^{7, 8}

The social network information (the interpersonal links between participants in the study) can also be used to estimate the effect of interventions and understand the mechanics of behavioural change. Diffusion of innovations and other behavioural change theories⁹ suggest that information is transmitted more effectively between people with strong social ties. Kelly and colleagues can test this theory by examining whether behavioural change varied according to the characteristics of the leaders, their participation in intervention training, and the strength of their relationship with participants. Of particular interest might be whether properties of network groups—such as density (the number of links) or centralisation (the degree to which those links are concentrated toward one or few people)—mediate leaders' effectiveness. Leaders in dense or centralised groups may have more power, influence, and control than those in sparse or decentralised groups.

So what are the challenges for future programmes? Scaling up of such interventions requires dedicated funding. Although the programme described by Kelly and colleagues reached hundreds of people at high risk, considerably more people are at risk.

A more widespread and cost effective method of communicating information on changing behaviour could be through the media, either by mass media broadcasting (television and radio) or the internet.¹⁰ However, it is unclear whether attempting to change behaviour via the internet is as effective as face to face interaction.¹¹ Although communication over the internet can be supplemented with extra material (references, links to testimonials), it is often unavailable for the most marginalised communities. Most people still prefer face to face interaction for behavioural change.⁹

Accumulated evidence from studies of behavioural change among doctors,¹² HIV and sexually transmitted

diseases, tobacco use, and substance misuse suggest that network data (surveys measuring who is connected to who) can be used to promote behavioural change.

The Roma men in Kelly and colleagues study were given the tools to promote behavioural change within their communities, and they showed that they were willing and able to do so. Healthcare professionals do their best work when they help communities realise their own potential for change. This study provides encouraging evidence of how that can be done.

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A model clinical trials agreement

The Department of Health's new model agreement raises questions about the NHS's relation with industry

Good clinical research is hard to do at the best of times, and there is a growing perception that the regulatory environment is making it increasingly difficult to plan and carry out clinical trials within a realistic time frame. A recent editorial in the *BMJ* claimed that the 2004 European Union clinical trials directive has hindered this process.¹ Anyone who has tried to carry out a clinical trial, particularly a multicentre one, knows only too well the frustrations of seemingly endless negotiations during the review process. While research may be a moral duty¹ in our search for better ways of caring, we must always be on guard

against using patients and volunteers as a means to an end, as the TGN1412 tragedy recently emphasised.²

On 30 October 2006, the Department of Health announced that a model clinical trials agreement had been finalised—a remarkable achievement that should be welcomed by all stakeholders in clinical research in the United Kingdom.³ This provides a template that



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can be used by all National Health Service trusts for any clinical trial, without modification.

The press release contained acclamation from leaders of industry and academia for what health minister Andy Burnham stated would “mean patients getting faster access to effective drugs and treatments,” a laudable goal. The benefits of not having to renegotiate many of the elements within clinical trials agreements for every sponsor, study, and centre are clear. Before embracing this agreement with open arms, however, we should examine what it actually says and what the deeper implications might be.

This agreement is not completely new, but a revision of a 2003 document,¹ and a concept that has now been examined in many jurisdictions.⁵ It applies only to contract research, defined as “commercial, industry sponsored trials of investigational medicinal products, involving NHS patients, undertaken in NHS hospitals, usually directed towards pharmaceutical product licensing.” It does not apply to phase I testing with healthy volunteers (as in TGN1412), to studies initiated by investigators, to trials in which the sponsor merely provides funding, or to research in non-NHS institutions. The announcement has received little comment to date, although links have appeared on some NHS trust websites. This lack of interest is surprising as the agreement is the product of a unique consortium of industry, government, and academia—the UK Clinical Research Collaboration (www.ukcrc.org).

In addition to industry, the collaboration lists an impressive collection of entities—referred to as partners—on its website, including government departments (Health, Trade and Industry), the NHS, the Medicines and Healthcare Products Regulatory Agency, the Academy of Medical Sciences, the Academy of Medical Royal Colleges, charities such as Cancer Research UK, the Medical Research Council, and the National Institute for Health and Clinical Excellence. The implication is that these bodies are equally committed to the agreement. Equally importantly, other organisations, such as the Central Office for Research Ethics Committees (www.corec.org.uk), are not mentioned. Research ethics committees are responsible for protecting human subjects² and are central to many issues covered in the agreement, such as budgets, financial disclosures, potential conflict of interest,^{3 4} compensation for research related injury, data protection, research publication, and research integrity⁵; the role of the committees is mentioned many times in the text of the agreement.

While collaboration is admirable, we must realise that the development of a business model for research is a primary motivation behind this initiative. The title of the collaboration’s press release refers to saving money and is therefore consistent with current NHS priorities.⁶ However, efficiency is not the same thing as effectiveness. It seems that the Department of Health⁶ and the NHS (www.rdforum.nhs.uk/) are fast turning into a business, as their current emphasis on research and development is in keeping with the chancellor’s prebudget statement.⁷ As the guidance document expresses it, the NHS is being “harnessed” in what is essentially a competitive model.^{8 9}

A surprising and disturbing element of the agreement relates to the crucial principles of transpar-

ency and accountability in research. Rather than incorporating and upholding the new and widely supported⁷ standards for an open research culture¹⁰ developed by the World Health Organization earlier this year,⁸ the clinical trials agreement has embedded an older and more problematic industry standard.¹¹

This model agreement appears at a time when public trust in the drug industry has never been lower.¹² The industry has recently been described as extraordinarily ineffective,¹³ and the *BMJ* (among others) has been urging that a firewall be set up between sponsors and research.⁹ The likelihood of guilt by association is therefore appreciable. For instance, were the royal colleges aware of this deviation from the international standard in transparency and accountability when they lent their name to the collaboration?

The concept of harnessing the NHS became even more problematic last month when the chief executive of the collaboration wrote to an assistant director general of WHO (WHO, personal communication); the support of all the partners was implied as their logos were attached. This letter complained about the scope of the WHO initiative on transparency and the alleged lack of consultation with stakeholders.

The removal of counterproductive roadblocks in research regulations is generally a good thing. Research is far more than just a business though. Regulatory review was created for compelling reasons and, no matter how important the research is, thoughtful analysis cannot be bypassed for the sake of convenience. The real benefits of contract research with investigational medicinal products should not be overstated.¹³ Association with money unfortunately erodes trust,^{10 13} however, and government and academia would be well advised to maintain a respectable distance from sources of funding.¹¹ The NHS is not for sale.

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