Neonatal screening for life threatening congenital heart disease

Routine pulse oximetry is an effective and low risk strategy

The linked study by de-Wahl Granelli and colleagues assesses the contribution of neonatal pulse oximetry saturation screening to early detection of life threatening congenital heart disease.\(^1\) Neonatal screening started in the 1960s with the Guthrie bacterial inhibition test for detection of phenylketonuria.\(^2\) Screening for this rare condition (about 1/12,000 live births) is almost universal in the developed world, and it illustrates the criteria for such a programme. Phenylketonuria can be reliably identified when asymptomatic, with a low false positive rate, and when treated early death or disability are prevented. Newer screening tests using techniques other than blood sampling should follow the same principles.

Critical congenital heart disease—cardiac malformations that are either ductal dependent or need surgery in the first month of life—occurs in about 170 per 100,000 live births. At first sight, universal pulse oximetry screening for this disease seems to contravene the above principles because clinical examination of the cardiovascular system is a part of the routine care of the newborn. However, clinical examination cannot reliably detect critical congenital heart disease. Cyanosis is poorly identified even when severe,\(^1\) and as many as 15% of babies with cyanotic critical congenital heart disease are discharged from their hospital of birth without being diagnosed.\(^3,5\)

Infants with critical congenital heart disease as a result of obstructive left heart lesions (including coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome) are even more difficult to diagnose,\(^4\) and they may present only when postnatal closure of the ductus arteriosus leads to acute and life threatening deterioration.\(^5\)

Infants diagnosed with critical congenital heart disease after discharge have a higher preoperative and perioperative mortality,\(^6\) so earlier detection may improve outcomes. Prospective studies have assessed whether this happens in practice. The most recent of these is the study by de-Wahl Granelli and colleagues, which assessed the introduction of universal oximetry screening in one region of Sweden.\(^1\) This study found a low false positive rate (0.17%) after the introduction of screening, and all infants with cyanotic critical congenital heart disease in the screened population were identified. Detection of left sided disease was more difficult, as in other studies, with five infants diagnosed after discharge. Nevertheless, fewer infants with such lesions were missed in the screened region. Evidence of benefit was seen even among the false positives—some of these babies had non-ductus dependent but serious congenital heart disease, mild heart disease, and pulmonary disease. The authors also identified 14 asymptomatic infants with high pulmonary artery pressures or right to left foramenal shunting; this is of more questionable benefit because such infants may be at one end of the normal spectrum and not in need of any intervention.

In contrast, a single centre study from the United States suggested that no additional infants were detected with pulse oximetry screening compared with the usual care at that hospital,\(^7\) which included close observation for four hours after birth before performing the screening pulse oximetry. This pattern of care is unusual in current practice and may have substantially increased the numbers of infants being diagnosed clinically. Other evaluations from the US have shown that 5-30% of affected infants are being discharged from their birth hospitals undiagnosed.\(^6\)

The best criterion for diagnosing critical congenital heart disease seems to be a lower limb saturation of less than 96% obtained from a new generation motion artefact resistant oximeter more than 20 hours after birth.\(^8\) Adequately trained screening technicians are needed and oximetry should last for at least 360 seconds.\(^2\) A saturation gradient of more than 3% between the infant’s right hand and a foot may be a useful indicator of left sided critical congenital heart disease.\(^4\) Some infants with this condition will be discharged without a diagnosis, so clinical signs of a possible cardiac defect must still lead to referral for full cardiac assessment, even if the infant had a negative screen.

In routine usage a false positive rate of the screening test somewhat higher than the reported 0.17-0.6% might be expected,\(^1,10\) especially during the introductory phase of a programme. High quality and rapidly available paediatric echocardiography services are essential for every baby who screens positive. This will require organisation and investment in paediatric cardiology services.

Education for parents and caregivers is also essential. A negative screening test does not completely rule out the possibility of serious congenital heart disease, and, because the prevalence of the screened condition is low, a positive screening test is more likely to be a false positive than a true positive. These characteristics are common among neonatal screening tests, and parents
Fish oil and secondary prevention of cardiovascular disease

The mechanism and size of any effect are uncertain

The National Institute for Health and Clinical Excellence (NICE) recommends that after a myocardial infarction patients should eat two to four portions of oily fish a week. People who are not willing or able to do this may be prescribed omega 3 acid ethyl esters, which are licensed in the United Kingdom and Japan for patients who have had a myocardial infarction. The aim is to achieve a daily intake of 1 g of long chain polysaturated fish oil and thereby to reduce the risk of death or further non-fatal cardiovascular events.

In the NICE review, evidence for the benefit of purified fish oils in this patient group was provided by one large trial completed a decade ago. GISSI (Gruppo Italiano per la Sperimentazione della Streptochinasi nell’Infarto Miocardico) found substantial reductions in total mortality and mortality from cardiovascular disease but not in non-fatal cardiovascular events. Important questions remained. Were the findings reproducible? Is it eicosapentanenoic acid, docosahexaenoic acid, or the combination of both that protects against recurrent cardiovascular disease? Are the benefits of fish oils greater than the now much better medical and surgical treatments for secondary prevention?

In the linked systematic review León and colleagues assess the effects of fish oil on the secondary prevention of mortality and arrhythmias, and whether a dose-response effect or formulation effect exist. Unfortunately, it does not provide answers to the questions above because little new high quality evidence is available. The review highlights the neglect of an important area of research into nutrient health, and hopefully it will lead to increased investment in research to resolve the uncertainty. Such research is needed not only because of the millions of people with heart disease worldwide, but also because the world’s marine fauna is being pushed towards extinction largely for commercial gain, but partly in the name of public health.

Since GISSI, only one randomised trial of omega 3 oils has been published that is large enough to generate more than a handful of fatal outcomes in patients with a history of coronary disease. The Japan Eicosapentanenoic Acid Lipid Intervention Study (JELIS) randomised 18 645 participants with dyslipidaemia (serum cholesterol ≥ 6.5 mmol/l)—regardless of disease status—to a statin only control group or statins plus 1.8 g eicosapentanenoic acid daily for about 4.5 years. It found that the addition of eicosapentanenoic acid reduced major coronary events by around a fifth. The trial also demonstrated the benefit of eicosapentanenoic acid without docosahexaenoic acid and eicosapentanenoic acid in addition to effective lipid lowering treatment.

The findings from JELIS are striking because fish consumption in Japan is high. Consumption ranged from 1.3 to 8.4 portions a week across quintiles of intake in the Japanese Public Health Centre cohort. High dose eicosapentanenoic acid reduced non-fatal coronary outcomes, particularly unstable angina, but it had no effect on fatal events, whether sudden death or fatal myocardial infarction. This evidence challenges the proposition, supported by the dramatic reduction in deaths from cardiac disease in a subgroup analysis


of GISSI, that the effect of fish oil is mainly the result of electrical stabilisation of the myocardium.

The anti-arrhythmia hypothesis is also challenged by the absence of clear benefit from fish oil supplemen-
tms in three trials of one to two years’ duration in pa-

tients with implantable cardioverter defibrillators.6 The results of JELIS suggest that the dose dependent
effect of eicosapentanenoic acid may be linked to a
sustained reduction in serum triglycerides that is dis-
tinct from the low density lipoprotein lowering mecha-
nism of statins. Eicosapentanenoic acid may also have
antithrombotic properties7; however, a reduction in
ischaemic stroke in JELIS was seen only in subgroup
analysis.8

The conflicting findings of GISSI and JELIS have
several potential explanations. The oil supplement
used in GISSI contained more docosahexaenoic acid
than eicosapentanenoic acid and differences in their
physiological effects may be important. The remark-
ably low background rate of fatal coronary disease in
Japan means JELIS, despite its size, was underpowered
to detect an effect of eicosapentanenoic acid even on
the combined end point of death from coronary dis-
ease. More than 10 times as many people died from
coronary disease in GISSI, with its 11324 participants
across Italy, than in the secondary prevention arm of
JELIS, with its 3664 participants. Indeed, León and
colleagues acknowledge that their meta-analysis of
mortality outcomes in those with existing disease is
dominated by GISSI.

The elephant in the room is that Japanese coronary
mortality is considerably lower than in Italy despite
Italy’s traditional Mediterranean diet. Japan’s low rates
of coronary disease may result mainly from the high
consumption of oily fish. It is thought that the fish ori-
ented diet protects the population as a whole from
cardiac death and those with higher fish intake from
non-fatal coronary disease.9 Other factors are also re-
levant, including the historically low prevalence of obe-
sity and related metabolic disorders, and the traditional
low calorie diet of which fish intake is a marker.

Valuable new evidence on fish oils and second-
ary prevention of cardiovascular disease will emerge
shortly in the form of the OMEGA study, which will
soon publish its findings.9 The likely higher rate of
fatal events in this German population will warrant an
update of León and colleagues’ meta-analysis.

Patient reported outcome measures in trials

Are widely available, but need to be standardised and used appropriately

The complete assessment of the benefits of an interven-
tion must include evidence of the effect on the patient’s
health status and quality of life. Such evidence is usually
based on self administered or interview administered
questionnaires, which are increasingly referred to as
patient reported outcome measures. Two linked papers
raise important questions regarding the standardised
application of these measures in randomised controlled
trials. The first used several patient reported outcome
measures as end points in an international study of
combined hormone replacement therapy.1 The second
is a systematic review of randomised trials that included
the short form 36 item (SF-36) health survey question-
naire as an outcome measure.2

Two broad types of patient reported outcome measures
exist—those that are specific to a disease or population
and those that are generic and can be applied across
populations, regardless of any underlying health prob-
lems.3 The two are complementary, the first type gives
detailed information about specific health problems and
the second type give more general information on health
and quality of life. Specific measures are usually more
responsive to changes in health after care for the health
problem being investigated.4 Generic measures have
greater potential to measure any unforeseen effects or
side effects of health care, and the results can be com-
pared with those for other populations. Generic measures
are also more suitable for use in economic evaluation.
These features have led to recommendations that both
types of measure are used in healthcare evaluations,
including randomised trials.

The SF-36 is a generic measure that was first tested in
the United Kingdom in the early 1990s and has since
become the most widely evaluated patient reported out-
come measure, with hundreds of published studies pre-
senting the results of testing for data quality, reliability,
validity, and responsiveness to changes in health.\textsuperscript{3,5} It is also the most widely reported measure within randomised controlled trials.\textsuperscript{2} Numbers of published studies related to disease specific measures have also grown immensely. Multiple measures exist for common health problems. This has led to confusion and different primary end points being selected across trials, which limits generalisability.\textsuperscript{3}

Given the evidence for the measurement properties of the SF-36, and its widespread acceptance and use, it makes a good generic measure of choice in randomised trials of health care that may affect health and quality of life. However, its use in randomised trials is not standardised, perhaps because potential users have to choose between eight scale scores and two summary scores.\textsuperscript{2} Many disease specific measures give a single score, but we still have the problem of defining what is an important or meaningful level of change that is needed for sample size calculations in randomised trials.\textsuperscript{5}

The exponential growth in patient reported outcome measures has not been matched by adequate consideration of their appropriate use and standardisation in randomised controlled trials. Recommendations that are based on expert consensus and systematic reviews of research evidence relating to outcome measures can promote standardisation.\textsuperscript{3,7} This work should follow the COSMIN (consensus based standards for the selection of health measurement instruments) standards for the selection of measures, which draws on existing recommendations and expert opinion.\textsuperscript{8} Many systematic reviews of patient reported outcome measures for different patient populations can now inform recommendations. Primary research that compares existing measures, which can further inform appropriate selection, should take precedence over developing new measures. Funding bodies should ask for documentation supporting the choice of patient reported outcomes, including evidence that the literature and available recommendations were consulted. The CONSORT statement should be amended to require supporting information on the selection of patient reported outcome measures and the proposed important level of change.\textsuperscript{9} These initiatives will contribute to the appropriate and standardised application of measures that include aspects of health and quality of life, end points that are of genuine importance to patients.

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Readmissions as a result of adverse drug reactions in older people

\textbf{Are related to comorbidity, but not advancing age}

In the linked retrospective cohort study, Zhang and colleagues explore which factors known to be associated with admissions for adverse drug events may place older people at an increased risk of readmission.\textsuperscript{1} Their retrospective study of older Australians showed that readmissions as a result of adverse drug reactions increased over a 13 year period and by 2003 comprised a third of the total admissions for these reactions.\textsuperscript{3} The mortality rate was 59.3\% in first time admissions and 68.1\% in recurrent admissions during follow-up (mean 4.2 years (SD 4.3)).

To study recurrent admissions for adverse drug reactions, all admissions need to be identified and then first admissions must be distinguished from recurrent ones. Zhang and colleagues identified recurrent admissions by scrutinising the 10 year period before the start of the study. Rigorously identifying all admissions is difficult when using retrospective data.

Correct coding of admissions for adverse drug reactions is complex and errors can occur at several stages. Knowledge of the drug’s safety profile is needed. Reactions that occur in 1:100 subjects should be well characterised at the time of licensing,\textsuperscript{3} but those occurring less frequently (<1:1000 subjects) or those affecting frailer patients excluded from trials may be identified only years later. Adverse drug reactions that affect the same system as the underlying condition are particularly difficult to recognise, as illustrated by selective serotonin reuptake inhibitors, which required an extensive review of the data to characterise the increased risks of suicidal ideation and behaviour.\textsuperscript{4} Increased awareness that centrally acting drugs affect suicidal risk has led to warnings being added to the product information of antiepileptic drugs.\textsuperscript{7}

Difficulties in identifying adverse drug reactions, differences in definitions and populations, and publication bias may all contribute to the large variations seen in hospital admissions attributed to these reactions. A meta-analysis of observational studies showed marked heterogeneity.
between studies, with larger studies generally reporting fewer admissions for adverse drug reactions (>5000 patients: <3% of patients had adverse drug reactions) than smaller studies (<1000 patients: 4-41% had adverse drug reactions). A review of prospective studies from the United States had similar findings (range 1-17%). A more recent prospective study in the United Kingdom may give a more accurate picture because of its large size and rigorous search for adverse drug reactions—all admissions to two Merseyside district general hospitals over six months were screened. It found that 1225 of 18820 (6.8%) admissions in people of 16 or over were caused by adverse drug reactions. The median age of those admitted for adverse drug reactions was 76 (interquartile range 65-83), which was significantly higher than those admitted for other reasons (median age 66 years, 46-79). According to Hallas methodology, 72% of reactions were classified as definitely or possibly avoidable. If three out of every four admissions for adverse drug reactions are potentially preventable what is the proportion for readmissions?

Despite an increasing awareness of the consequences of adverse drug reactions, both to the individual and healthcare provider, little is known about factors that increase the risk of readmission. Zhang and colleagues compared comorbidities between patients readmitted with adverse drug reactions and first presenters. Increased hazard ratios were associated with comorbid congestive cardiac failure, peripheral vascular disease, chronic pulmonary disease, rheumatological disease, liver disease, renal disease, diabetes, and malignancy. Although the ratios were small they increased with the severity of the comorbidity, as would be expected. The point estimate for the hazard ratio for mild liver disease was lower than for moderate-severe disease (1.48, 95% confidence interval 1.05 to 2.07 v 1.85, 1.18 to 2.92) as was that for mild-moderate diabetes (1.18, 1.07 to 1.30) versus diabetes with chronic complications (1.91, 1.63 to 2.22). No increased risk was seen with greater age.

The findings should be interpreted with caution in view of the retrospective nature of the data (only 60% of comorbidities were recorded), but the associations may represent increased frailty in those readmitted. Chronological age is not a good prognostic indicator in many conditions in elderly people because the oldest may be a cohort of survivors with healthier constitutions. Frailty is more closely linked with poor health outcomes, including adverse drug reactions. Many of the associations seen by Zhang and colleagues place the individual at increased risk of further reactions because of reduced drug elimination. This study is one of the first steps in identifying those at increased risk of readmission from adverse drug reactions. Interventional studies are needed to ascertain whether readmissions as a result of adverse drug reactions in the elderly can be prevented. However, Zhang and colleagues’ study should raise awareness of the increased risk of continuing polypharmacy in patients with comorbidities that may impair drug handling. The balance between continuing medication and risk of further reactions cannot be judged from these data, but an admission for an adverse drug reaction should prompt a full medication review to look at the need for each drug and its dose.


Changing behaviour through state intervention

When does an acceptable nudge become an unacceptable shove?

The question of when governments should intervene to change our behaviour sits at the heart of political philosophy and bioethics. In their recent book, *Nudge: improving decisions about health, wealth, and happiness*, Richard Thaler and Cass Sunstein argue that public and private organisations can and should intervene more often than they currently do to alter people’s behaviour. Their thesis is based on the observation that people often behave in ways that are not in their best long term interests. The remedy, they argue, is to present options in such a way as to increase the likelihood that people will choose what they would, on reflection, most prefer. This approach has attracted much interest and support from politicians including Barack Obama and David Cameron.

Thaler and Sunstein call their general approach “libertarian paternalism”—paternalistic in that governments, for example, play an active role in framing options, but libertarian in the sense that people ultimately remain free to choose. Examples of such approaches in the health context include placing fresh fruit and vegetables at the

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front of canteen displays, requiring people to purchase permits if they wish to buy cigarettes, and organising organ donation under an opt-out rather than an opt-in system. Related schemes include using financial and other incentives to encourage smokers to quit and to increase the likelihood that patients with schizophrenia will take long acting medication. These approaches can have a great impact on people’s behaviour.

The extent to which such interventions may be adopted depends not only on their effectiveness but also their acceptability. Although some people see such interventions as acceptable “nudges,” others consider them unacceptable “shoves.” The debate then revolves around whether the paternalistic or libertarian aspect of libertarian paternalism dominates. Its resolution turns in part on how we understand people’s behaviour, and whether it is possible or worthwhile to distinguish conceptually and empirically between these two forms of pushing.

People’s behaviour is a function of their values and their environment. Even when people are not forced to act in particular ways they often choose options that, on reflection, they wish they had not. For example, most smokers would prefer not to smoke, and most overweight people want to lose weight. How do we understand this apparent irrationality? Two behavioural principles seem to be operating. Firstly, the environment has a far larger effect on our behaviour than we acknowledge. This lack of acknowledgment reflects a behavioural principle that has been termed the fundamental attribution bias, in which we perceive our behaviour as determined more strongly by our dispositions than by situations, a bias that is seen across cultures, patients, healthcare professionals, and policy makers.

Behaviours that are immediately rewarding, such as eating chocolate cake, are more likely to occur than those that bring delayed rewards, like running across a park. The rewarding nature of immediate gratification reflects the second behavioural principle that helps explain why people often act in ways that do not reflect their long term goals or interests. Unfortunately, the health costs of many behaviours occur in the future, whereas their benefits are enjoyed in the present. The so called obesogenic environment reflects the operation of these two principles—that is, an environment that contains a plethora of readily realised options that offer immediate gratification but that cause and sustain obesity.

Any attempt to disentangle nudging from shoving requires operational definitions. Nudging could be defined as increasing the chances that people act in ways that, on reflection, they would have chosen themselves; this is variously described as acting on preferred preferences or acting consistently with deeply held values. Shoving can be defined as increasing the chances that people behave in ways preferred by the “shover” but not the “shoved.”

Evaluating interventions against these definitions requires the development of measures of values, immediate and considered preferences, as well as coercion, to be used in the context of robust experiments evaluating the effect of interventions designed to nudge.

So, for example, in the context of food labelling, different sets of nutritional labels might be compared for their effect on food purchased and, more importantly, the extent to which it matches the food people say that they would prefer to have bought after careful deliberation.

Finally, it is worth considering in a health context whether distinguishing between nudges and shoves is useful. Thaler and Sunstein show that our choices are invariably structured, but that we are often unaware of this, and pay scant regard to the fact that the choices we make are frequently inconsistent with our “preferred preferences.” This is perhaps the key message. Policy makers and public health practitioners in particular should perhaps be less concerned with discussing liberty and paternalism and be more concerned with trying to structure environments to achieve choices that, on reflection, are endorsed by the chooser. At the heart of this is a paradox—acting paternalistically to achieve liberty. Failure to engage with this means that we may remain slaves to the environments we often have little part in shaping.

Perhaps the best nudge provided by Thaler and Sunstein’s book is towards a debate about the political philosophy that should guide governments wanting to improve the health of their populations.