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Inactivity, disability, and death: all interlinked

If you must watch a lot of television, move during commercial breaks—every little helps

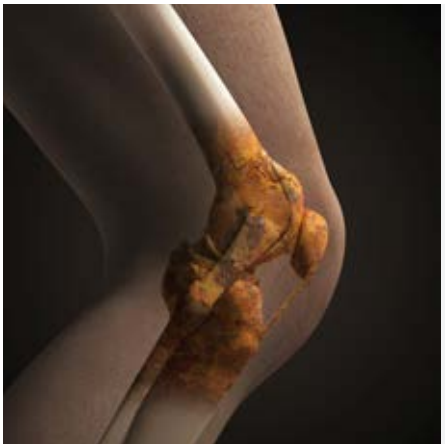
Elizabeth Badley professor, Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, ON, Canada, M5S 1A8
E.Badley@utoronto.ca

Physical activity has long been recognised as an important determinant of health and longevity, and many countries have explicit physical activity guidelines for promoting health.[1 2] The corollary of this is that people who do not meet the guidelines, a substantial proportion of the population,[3] are at risk of worse health. However, relatively little attention has been given to the question of how much activity is needed to make a difference.

Although this was not their main aim, two new papers shed light on this question. Dunlop and colleagues followed a cohort of people who had mild to moderate osteoarthritis or were at risk of osteoarthritis to look at the development of disability over two years.[4] Cooper and colleagues estimated the relation between physical capability in midlife—as indicated by grip strength, chair rise speed, and standing balance—and later mortality.[5] Both showed that the relation between inactivity and risk of disability or death is not linear: people in the extreme lowest of the low categories for physical activity or capability were at disproportionately greatest risk.

Dunlop and colleagues' study followed a cohort of older adults with a mean age in the early 60s for two years. Three quarters of their participants were overweight or obese. Physical activity was measured objectively using an accelerometer, and participants were assigned to one of two categories of activity: non-sedentary activity of light intensity and activity of moderate to vigorous intensity. This was a very sedentary cohort that averaged about 20 hours a day with no activity, and any activity reported was overwhelmingly in the light intensity category.

Almost 15% of those in the lowest quarter of activity developed disability over two years, compared with well under 10% of those in the other three quarter groups. Although the development of disability could arguably be due to osteoarthritis, not all cohort members had symptoms, and the authors were able to control for other musculoskeletal symptoms and selected comorbidities including cancer and heart disease. The disproportionately high risk for the lowest quarter held when other predictors of disability and time spent in moderate to vigorous activity were controlled for.



More is at stake for inactive people with osteoarthritis than just an increased risk of disability; mounting evidence shows that osteoarthritis is associated with increased mortality

The paper by Cooper looks at the physical capability of people aged 53 enrolled in the 1946 British birth cohort and relates this to mortality over the next 13 years. Trained nurses used a standard protocol to assess three physical capability measures—grip strength, chair rise speed, and standing balance time—and a composite measure was derived by combining the score on these measures.

The mortality rate was more than five times higher for people in the lowest fifth of the composite score compared with those in the highest fifth. The excess risk was even higher for those who could not perform the individual measures at all. The relation still held after adjustment for other variables likely to be associated with mortality. As in Dunlop and colleagues' study, the difference between the lowest and highest fifths was much greater than the difference between the highest and other fifths. Both sets of authors note that the excess risk in the lowest quarter or fifth may represent the influence of subclinical disease and the aging processes even in midlife, as well as lifetime exposure to physical activity, smoking, and an unhealthy diet.

A major limitation of Cooper and colleagues' paper is that the specific health problems that prevented participants from being able to perform each test were not recorded. This deficit was remedied at a later follow-up examination of this cohort when, as expected, commonly reported reasons included diseases of the musculoskeletal system.

Juxtaposing the two papers, lack of physical activity among adults with osteoarthritis (the most common type of arthritis[6]) is associated with the development of disability and likely associated reductions in physical capability.[7] Reduced physical capacity in turn compromises life expectancy. In other words, more is at stake for inactive people with osteoarthritis than just an increased risk of disability. Mounting evidence shows that osteoarthritis is associated with increased mortality[8]; perhaps more thought needs to be given to the role of physical activity in this context.

Target interventions at lowest activity group

Many of the previous studies on the relation between physical activity and disability or death have been confined to older adults.[7] These new papers focus on people in the middle years of life and those with low activity or physical capacity levels. In both papers, although a gradient with increasing activity exists, the excess risk for disability or death in the lowest activity group is notable and suggests that this group should be a priority group for intervention.

The good news is that increasing activity just a little could pay dividends. For example, on the basis of data from Dunlop and colleagues' study, increasing light intensity activity by just over an hour a day might do the trick for people in the most inactive group. Among adults who watch a lot of television, for example, this might be achieved by moving around during commercial breaks. An underlying message of these papers is that every little helps.

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RESEARCH, pp 11, 12

Industry funded studies can be of higher quality than studies undertaken by non-commercial sponsors, and scrutiny by regulatory agencies further helps to identify limitations in the quality of trials

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Trials of autologous bone marrow stem cells for heart disease

A disappointing research effort characterised by errors, inflated effect sizes, and lost opportunity

Nick Freemantle professor of clinical epidemiology and biostatistics nicholas.freemantle@ucl.ac.uk
Greta Rait senior lecturer, Priment Clinical Trials Unit, Research Department of Primary Care and Population Health, UCL Medical School, London NW3 2PF, UK

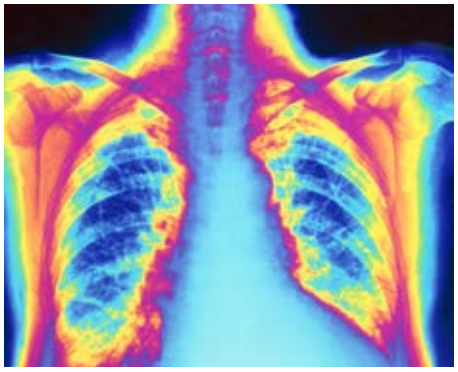
The report by Nowbar and colleagues on the relation between the number of discrepancies observed in clinical trials of autologous bone marrow stem cells for ischaemic heart disease and ejection fraction includes shambolic and poorly conducted research that reflects poorly on every part of the research process.[1] On average, trials with many errors show improved ejection fraction, while trials with no errors find no benefit.

How should we react to this finding and what lessons can we learn? In *An Essay on Criticism*, Alexander Pope stated that "to err is human," but surely there is no place for errors in development of evidence that will inform treatment decisions?[2]

Errors range from the unfortunate typo to poor design, conduct, analysis, and reporting. Many of the errors could be explained and are perhaps less harmful than Nowbar and colleagues imply; their description of "impossible" percentages being an example. The chameleon nature of some of these studies, which seem to be randomised trials in one paper and then are described as "acceptor/rejecter" studies in other related publications, is worrying. Not all of these "trials" were listed in trial registers. Although the authors draw back from classifying errors into a hierarchy, it is important to understand how serious errors are, as well as how often they occur, when one is appraising a trial.

Who is responsibile for uncovering errors if the trial investigators are careless or ignorant of design and analysis issues? Not the doctor, who might wrongly presume a degree of protection from a peer reviewed publication when counselling a worried patient. Positive results for new treatments can easily influence the decision to publish, even if samples are small and methods less than ideal. An editorial can highlight these concerns but invariably a weak study will be quoted more often than its cautionary editorial. The online facility of journals should at least allow for rapid correction of errors after publication and for continued debate.

Trials with positive results might generate more publications than those with neutral results, and the number of errors might be associated with the number of pages in print describing a trial. But opportunity for error is not a valid mitigation. Trials are ultimately simple in principle (although often complex in implementation). Randomising patients between experimental conditions limits bias as long as we measure outcomes objectively and keep tabs on all our patients (both easier said than done). Given modern reporting standards for clinical trials,[3] we might have thought that getting it right, or at least nearly so, was achievable. More than 20 years ago, Ken Schulz and colleagues identified the relation between poor reporting and inflated effect sizes.[4] Surely it should not take two decades to learn such a basic lesson?



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Omnishambles

Why the rigours of market authorisation help

Unlike other biotechnologies, such as insulins, there are no obvious large scale commercial sponsors for trials of autologous bone marrow stem cells and therefore no coherent programme of evaluation aimed at market authorisation. We recognise that industry funded studies can be of higher quality than studies undertaken by non-commercial sponsors,[5] and scrutiny by regulatory agencies further helps to identify limitations in the quality of trials. This kind of scrutiny is largely missing from non-commercial trials, when the sponsor is not seeking market authorisation. Recent developments in the United States and Europe suggest that we might be moving to a more robust regulatory process for autologous bone marrow stem cells,[6 7] which is a welcome development, although only one part of the answer.

Regulatory influence in cardiovascular trials has arguably led to harmonisation of design and outcome measurement across trial programmes. In particular, the composite outcome of death and cardiovascular admissions has proved helpful in drug and device development.[8 9] Appropriate length of follow-up in suitably high risk populations is also required if major morbidity and mortality outcomes are to be estimated with precision. Although several trials of autologous bone marrow stem cells included mortality as a secondary outcome measure, none were adequately designed to provide a useful estimate of the difference in the rates of death between the randomised groups.[10] Regulation, however, is only half the answer, with proper funding and trial sponsorship also required to amass sufficient evidence on safety and effectiveness to support use in routine practice.

The almost total absence of any coordination or strategic thinking is a further problem. Nowbar and colleagues' review included 49 studies,[1] the number and design of which illustrate the lack of organisation and coordination. Half the trials include fewer than 50 randomised participants, and none have more than 400. Surely these resources could have been used more efficiently to generate fewer, larger confirmatory phase III trials following on from a proper phase II programme, including a few smaller studies on dose finding and proof of principle?

We could have progressed so much further, either to identify a worthwhile treatment and the patients who are likely to benefit or, equally valuably, to discover that treatment with autologous stem cells is futile or unsafe. Failure to take this opportunity arguably lets down trial participants, who might reasonably believe that they were advancing science by agreeing to randomisation in clinical trials. This lost opportunity also lets down potential patients, the doctors who care for them and suggest treatment options, and of course tax payers and charitable givers whose scarce resources have been wasted.

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- Practice: Should children who have a cardiac arrest be treated with therapeutic hypothermia? (BMJ 2014;348:f7672)
- News: European research is launched into hypothermia stroke treatment (BMJ 2012;344:e2215)
- Head to head: Does the evidence support the use of mild hypothermia after cardiac arrest? Yes (BMJ 2011;343:d5830) No (BMJ 2011;343:d5889)

Inducing hypothermia after out of hospital cardiac arrest

Latest large trials provide no support for this intervention

Stephen Bernard senior specialist, Intensive Care Unit, The Alfred Hospital, Melbourne, VIC 3004, Australia
s.bernard@alfred.org.au

Out of hospital cardiac arrest is common and is associated with a high rate of mortality.[1] With early ambulance treatment, about 30% of these patients have a return of spontaneous circulation and are transported to hospital. However, many patients remain comatose owing to hypoxic brain injury, and this is the leading cause of death after hospital admission.

Over the past decade, there has been considerable interest in the use of therapeutic hypothermia, where patients are cooled to a target temperature of 32-34°C and this temperature is maintained for 12-24 hours. This approach is based on the results of two clinical trials published in 2002.[2 3]

More recently, a larger trial compared a target temperature of 36°C with that of 33°C.[4] The Targeted Temperature Management (TTM) trial randomised 939 patients who remained comatose after resuscitation from out of hospital cardiac arrest at hospitals in Europe and Australia. The primary outcome measure was all cause mortality at the end of the trial. Overall, 50% of the patients in the group allocated to 33°C for 24 hours died compared with 48% of those allocated to the 36°C group (hazard ratio 1.06, 95% confidence interval 0.89 to 1.28; P=0.51).

This clinical trial was well conducted and the conclusion was clear—patients who are comatose after resuscitation from out of hospital cardiac arrest do not benefit from lowering the body temperature to 33°C. The inclusion and exclusion criteria were appropriate, the allocation to the treatment arms was blinded, the target temperatures were clearly separated in the two groups, and the outcome assessment was robust. None of the predefined subgroups, including patients with initial ventricular fibrillation, showed any suggestion of benefit from a temperature target of 33°C compared with 36°C.

There were several notable differences between the 2002 trials and the TTM trial. In the HACA trial (one of the 2002 trials), patients in the control group had modest fever (~37.5°C) during the first 24 hours of treatment, but it is uncertain whether such a small increase in temperature would lead to dramatically worse outcomes. Another important difference between the two sets of trials was that in the TTM trial there was a protocol driven approach to prognostication in patients who remained comatose after initial treatment. In the TTM trial, there was a delay of 108 hours from admission to when the clinician considered the prognosis. Importantly, recommendations for palliative care were made by clinicians who were blinded to treatment allocation. This is in contrast to the 2002 trials, in which the approach to withdrawal of active treatment was not explicitly defined and may have been made earlier and by clinicians aware of treatment allocation. Patients in the 2002 trials allocated to the active intervention may therefore have received palliative care less often.

Attention should now turn to rigorous investigations of other aspects of care after cardiac arrest that have been proposed for this patient group

ADRIENNE HART-DAVIS/SPL

There was a delay of several hours between patients being resuscitated and reaching the target temperature in the TTM trial. However, this was also the case in the 2002 trials, and it occurred in the recent study despite the use of more modern cooling devices. It is possible that earlier cooling would be more beneficial, although other studies of early therapeutic hypothermia using bolus ice cold saline immediately after resuscitation found no benefit with earlier cooling.[5-7] In the trial by Kim and colleagues, 1367 patients were randomised after resuscitation to standard care or cooling using bolus ice cold intravenous fluid during ambulance transport to hospital. The actively cooled group experienced rearrest during transport more often than the control group (26% *v* 21%; P=0.008), and there was no difference in outcomes at hospital discharge.

Nevertheless, very early therapeutic hypothermia may still have a role in these patients. Two clinical trials are currently testing the effect of the induction of hypothermia during cardiopulmonary resuscitation using bolus ice cold intravenous saline or nasopharyngeal cooling.[8 9]

Until the publication of the TTM trial, patients who were comatose on arrival at the emergency department after an out of hospital cardiac arrest received sedation and muscle relaxation, followed by surface cooling using cold water jackets and blankets in an effort to lower core temperature rapidly. In some hospitals, adherent surface cooling pads or intravascular cooling catheters are used to induce therapeutic hypothermia. These are expensive, and it is difficult to transport such equipment to the cardiac catheterisation laboratory before admission to the intensive care unit. Clearly, a target temperature goal of 36°C is simpler, cheaper, and easier to manage.

No so cool

Thus, the TTM trial should change practice immediately. The compelling evidence from the TTM trial is that patients who have been resuscitated from an out of hospital cardiac arrest and who remain comatose should not receive therapeutic hypothermia (32-34°C) after admission to hospital. Instead, a temperature target of 36°C is appropriate and much more easily achieved. Importantly, prognostication in such patients should be delayed for at least 72 hours after sedation is stopped, except in cases of brain death or early myoclonus with bilaterally absent somatosensory evoked responses. In addition, there seems to be no supportive evidence for active cooling using ice cold intravenous fluid bolus in the prehospital setting.

Attention should now turn to rigorous investigations of other aspects of care after cardiac arrest that have been proposed for this patient group. These include avoidance of hyperoxia,[10] vigorous support of blood pressure,[11] and early cardiac catheterisation of patients without ST elevation myocardial infarction.[12]

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- Editorial: Improving mental health services in England (BMJ 2014;348:g1907)
- Analysis: Reform reform: an essay by John Oldham (BMJ 2013;347:f6716)
- Views & Reviews: NHS "reform" in England: where is the public interest? (BMJ 2012;344:e2014)

Transforming healthcare: necessary but difficult

Recent King's Fund report on mental health services provides some useful pointers

Carole Kaplan transformation programme director
carole.kaplan@ntw.nhs.uk
Elizabeth Moody group nurse and transformation programme director
Stewart Gee programme manager, Northumberland Tyne and Wear Foundation Trust, St Nicholas Hospital, Newcastle upon Tyne NE3 3XT, UK

Once again, changes are needed in the health service. The impetus comes from concerns about the quality and safety of services, combined with the need to save money. Although transformations are already widespread in the NHS, there is little consistency in approach, with recent reports of advances as well as retreats.[1]

What can we learn from previous large scale transformations in the provision of healthcare? Recently, the King's Fund summarised lessons from the radical transformation of the UK's mental health services—from a service based in institutions to one based in the community. Its summary is augmented by reports of two workshops attended by people with experience of transformation. What is interesting is how consistently their messages are reflected in informal discussions across the country.

As the King's Fund report makes clear, change is a constant feature within public services. But if transformation is to succeed in increasing quality and reducing costs sustainably, many problems need to be dealt with. Doctors need to be able to identify waste in the system and accept that the old ways are not necessarily the best ways. Ultimately, they need to believe that any change adds value for the patient.[2]

Many trusts want to increase time spent in patient contacts and reduce time spent on non-value adding tasks that could be done differently, such as administration, attendance at meetings, and travel.[3] The burden of non-clinical work is often the source of complaint, and if this could be reduced, clinicians could focus their expertise on patients. Recent technological advances, such as digital dictation and mobile technology, have reduced time spent on administrative tasks. Referrers and patients can both receive information more quickly and reliably, and telemedicine may bring further benefits. In psychiatry, senior staff are often engaged in tasks that could be done as well by other staff, and resources such as peer support workers and patient led recovery systems can help to ensure that different elements of care are delivered by staff with the appropriate skill levels.[4]

Few clinicians have experience of managing organisational change, and many find it difficult. This is in marked contrast to their routine clinical work, where getting patients to change is often the focus. Change driven by patient oriented values may be easy to articulate, but can be hard to implement.[5]

In industry, transformation is regarded as a continuous process, but this is rarely the case in the health service. As a result, insufficient attention has been given to reducing or removing tasks that do not add value for the patient. We believe that full scale transformation benefits from a systematic approach. The theory of change management, despite its limited evidence base, provides a useful framework.

Engagement of patients and carers, as well as clinical staff and partner organisations, is fundamental. The sense of ownership of any newly devised model is essential for success.[6] Communication with those not directly involved in the creation of the new model is key, but communication is not the same as engagement, which is far more difficult to achieve. A methodology to support the process of change is useful, but so is knowledge of the likely reaction to change, particularly among those who have to implement it.

Don't give me grief

Each person reacts differently to change, experiencing a range of emotions as described in the variously adapted versions of the Kubler-Ross model of grief.[7] Change may provoke high levels of anxiety at both institutional and personal levels, which can both promote and impede transformation.[8] A clear and well supported workforce strategy is therefore essential. Adoption of a clear legal framework in relation to employment law and acceptance by management of the inherent risks of any change is important.

Change is difficult and can become an all consuming exercise. Care must be taken to ensure that there is a balance between instituting the change and safely delivering "business as usual." Gilburt and colleagues discuss "double running"—continuing with the old model while piloting the new one—as one way to achieve this.[6] Although this is costly and complex, it may be a safer option, because it enables new designs to be evaluated scientifically. However, it is worth remembering that service innovation goes on all the time in the health service and is not evaluated with this kind of rigour.

"Parity of esteem" between services is required,[9] and commissioners need to be actively engaged in the process of remodelling so that an understanding of any new clinical system informs their allocation of funding. A clear evaluation of service implementation is essential. It should be coherent not only regarding patient pathways, but also in the wider health and social care economy. This would enable the measurement of benefits to patients, carers, and healthcare staff. It could also provide metrics regarding the impact on services such as housing, local authority facilities, ambulance services, and others. In mental health services there are many examples of specialist welfare advice being provided piecemeal, and suggestions that these be incorporated into care pathways from early in the design stage may lead to an improved collaborative model that is far more efficient.

We agree with Womack and Jones that many healthcare debates in the political arena are a cost shifting or service elimination contest, as the various parties along the value stream try to defend their own interests at the expense of others.[2] Services for both mental and physical health have a lot to learn about transformation, and resources should be made freely available to the whole health and social care environment.

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