Improving fitness and reducing obesity in preschool children

Multidimensional interventions can be effective in migrant populations

We are now in the midst of a global obesity epidemic that extends into early childhood; the World Health Organization estimated in 2010 that more than 42 million children under the age of 5 were overweight. Excess fat gain during this crucial developmental period can lay the groundwork for adverse psychological, social, and health outcomes. During the preschool years children approach an “adiposity rebound”—a rise in body mass index that occurs between 3-7 years—the timing of which determines the probability of developing obesity later in life. Of particular concern is the comparatively high prevalence of overweight and obesity among children from migrant communities and socially disadvantaged backgrounds. Finding ways to reduce the burden of obesity in these high risk populations is a key priority in many counties. In the linked randomised trial, Puder and colleagues assess the effect of a multidimensional lifestyle intervention on aerobic fitness and adiposity in predominantly migrant preschool children.

Poor aerobic fitness has been suggested as an important contributor to obesity in early childhood. Although several cross sectional and longitudinal studies have noted inverse associations between cardiorespiratory fitness and total adiposity in older children and adolescents, data about these associations in preschool children are scarce. Furthermore, randomised controlled trials from which a cause and effect association between fitness and obesity in this age group can be determined are lacking. An increase in fitness probably has a protective effect on obesity, but children with excess adiposity may also reduce their physical fitness through a mediating factor, such as a decrease in overall physical activity.

Puder and colleagues show positive effects of a multidimensional lifestyle intervention on aerobic fitness and adiposity in more than 600 predominantly migrant preschool children living in Switzerland. The study, which targeted teachers, children, and parents over one school year, focused on physical activity, nutrition, media use, and sleep duration. A key element of the intervention was the consideration of multiple environmental and individual influences within the social ecological model. Compared with the control group children receiving the intervention had a significant increase in aerobic fitness (11%) and significant decreases in percentage body fat (5%), sum of four skinfolds (10%), and waist circumference (2%).

These findings offer hope for future public health campaigns that aim to tackle lifestyle disease in young migrant populations. The size of the improvements seen here would have considerable implications not only for overweight and obesity, but also for the many metabolic and psychosocial risk factors related to poor aerobic fitness, including high cholesterol, hypertension, insulin resistance, depression, and anxiety.

The study builds on recent research that targeted low socioeconomic preschool children, parents, and nursery school teachers in a comprehensive 12 month nutrition and physical activity intervention. The cluster randomised controlled trial, which investigated 725 children, showed a significant improvement in fitness (percentage improvement not stated) and a 32% reduction in the number of overweight children. A common thread between these two successful interventions is that the focus extended beyond the individual child to encompass multiple dimensions of the preschool and home environments. Another similarity is that both interventions were maintained for a full school year. Taken together, these studies indicate that a considerable investment of time and resources is needed to achieve meaningful health improvements in high risk preschool children. Whether or not such improvements are sustained into the school years remains to be seen.

Puder and colleagues’ study also provides insight into the cause and effect association between fitness and obesity in preschool children. Despite the significant increase in fitness, the authors found no changes in objectively measured physical activity. This indicates that the beneficial effect of fitness on adiposity was not mediated by an increase in overall physical activity, and it justifies a specific focus on aerobic capacity as an obesity prevention strategy. It is also a reminder that young children should be regularly supported to engage in vigorous activities in addition to light or moderate play.

The findings of Puder and colleagues’ study are promising, and there is ample scope for future research in this area. The number of interventions focusing on fitness or obesity (or both) in older children greatly exceeds that in preschool children, and it is difficult to generalise the results from successful school based interventions, given the marked differences in cognitive and physical development and environmental influences on behaviour between these age groups. Little is known about how aerobic fitness and reduced adiposity in early childhood are related to other health indicators during growth and maturation. In addition, the short term and long term cost effectiveness of preschool interventions is largely unexplored. Although it can be assumed that any sustainable improvements in fitness or obesity will yield health benefits as children progress into adulthood, the likelihood that individuals will maintain these changes and the public health savings associated with a reduction in disease risk requires further research.
Mobile telephones and brain tumours

Evidence is reassuring, but continued monitoring of health registers and prospective cohorts is still warranted

In the linked cohort study, Frei and colleagues found no evidence that the risk of brain tumours was raised in 358403 Danish mobile phone subscribers. This was also true when the cohort was restricted to people who had been subscribing for more than 10 years, when gliomas and meningiomas were analysed separately, and when tumours in the anatomical region closest to the handset were analysed.

The study has two important methodological advantages over most other studies. Firstly, it was based on a computerised cohort that was followed passively in registries, so it avoided the need to contact people. Consequently the problem of non-response and selection bias—which has been of considerable concern in studies with other designs—was eliminated. Secondly, it used digitised subscriber data obtained from the operators rather than retrospective questionnaire or interview information obtained from users. This circumvented the recall bias that is present in other studies.

One weakness, however, was that having a mobile phone subscription is not equivalent to using a mobile phone and conversely some users will be non-subscribers. The resulting misclassification would dilute any association between mobile phone use and cancer risk, and this is important for a negative study like the current one. However, for long term users, this misclassification would have only a small effect: long term users who did not hold personal subscriptions would make up a small proportion of the reference population.

Frei and colleagues’ results may seem reassuring, but they must be put into the context of the 15 or so previous studies on mobile telephones and cancer. Although most of these studies were also negative, there are a few exceptions. A Swedish group has repeatedly reported that mobile phone use is associated with an increased risk of brain tumours. Among the results reported by this group were increased risks after only five years of mobile phone usage. This is a problematic finding because with such a short time between the start of phone use and clinical disease, an effect—if there were any—would have been detectable in national cancer statistics, but it was not (figure).

This casts doubt on the methodology used by this research group.

The other major divergences from the overall negative literature are some findings in the Interphone Study, a multicentre brain tumour case-control study carried out in 14 countries. Overall, and in most subanalyses, mobile phone users were not at increased risk of cancer. However, an increased risk was seen in the highest exposure category (the top tenth). In contrast, risk was decreased in the second to highest exposure category, being among the lowest of all categories.

National cancer statistics for Sweden are available up to and including 2009 (figure). Generally, aggregate data are much less informative than data from analytical studies. But in the case of mobile phone use, the proportion of users has...
increased so rapidly and reached such high numbers that aggregate data are highly informative. The graphs show that the incidence rates for glioma have not risen since 1970. Handheld mobile phones were introduced in Sweden in 1987 and usage spread quickly. In fact, 87% of 16-75 year olds were mobile phone users in 2002.20 Thus, almost 90% of the population had been using mobile phones for at least seven years in 2009, and the proportion that had been using them for 10 years or even 15 years must have been substantial. Hence, the absence of a trend in the incidence of brain tumours in national statistics is reassuring.

The search for an association between mobile telephone use and cancer risk should be viewed in the context of its origin. It did not originate from a particular biophysical hypothesis or results of a seminal study but from a concern that some aspect of the interaction between radiofrequency fields and human physiology has been overlooked or misunderstood. The research that has been conducted for the safety of public health with regard to this new and rapidly spreading technology is now extensive. The question is how much more research is needed. Continued monitoring of health registers and prospective cohorts is warranted, but more case-control or other studies with built in selection and recall bias are not needed.

Cost of dabigatran for atrial fibrillation

Cost effective in patients at high risk of stroke, unless INR is well controlled

Because atrial fibrillation is associated with advanced age and obesity, its prevalence is increasing worldwide.3 New treatments such as ablation and left atrial occlusion may reduce the need for anticoagulants in highly selected patients with atrial fibrillation, but overall the use of anticoagulants will increase in the foreseeable future. In the linked study, Pink and colleagues assess the incremental costs and benefits of dabigatran etexilate versus warfarin in patients with non-valvular atrial fibrillation.4

Until recently, warfarin and related vitamin K inhibitors have been the only oral anticoagulants available. Warfarin is cheap and effective, but it doubles the risk of haemorrhage, requires careful monitoring, and has many drug interactions.5 Compared with warfarin, dabigatran has a wide therapeutic index, so no monitoring or dose adjustment is needed (except in patients with renal disease). Dabigatran works by inhibiting thrombin directly, so its onset of action is rapid, unlike warfarin. To date, dabigatran is the only new oral anticoagulant approved for atrial fibrillation in several countries, including the United States. Thus, dabigatran has the potential to be widely prescribed.

The potential economic consequences of widespread use of dabigatran rather than warfarin are profound. For example, on the basis of Pink and colleagues’ data, if all of the approximately 760 000 British patients with atrial fibrillation took dabigatran (at £919.80 (€1051; $1471) per year), the drug cost would be £700m each year, but expenditures related to stroke and warfarin monitoring would shrink. Given the potential financial effects of dabigatran, the cost effectiveness analysis by Pink and colleagues is timely and relevant.6

The authors use a Markov decision analytical model to discount future events, to extrapolate from the two year RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial,3 and they compare various health states using a well accepted metric, quality adjusted life year (QALY). In the base case, they calculate an incremental cost effectiveness of £23 082 per QALY. The advantage of QALYs is that this metric provides a common currency to account for complications of atrial fibrillation and its prophylaxis. Clinicians may feel uncomfortable extrapolating from a two year trial to a lifetime horizon, but no long term data are available for dabigatran. This extrapolation is therefore needed for Pink and colleagues to calculate the downstream consequences of stroke and stroke prophylaxis.

Although stroke is the most feared consequence of atrial fibrillation, prevention of stroke also has serious risks. The most important risk of prophylaxis is haemorrhage, especially intracerebral haemorrhage, which is lower for treatment with dabigatran than with warfarin. In RE-LY, rates of intracerebral haemorrhage (per 100 patient years) were 0.30 with dabigatran 150 mg twice daily and 0.74 with warfarin.3 By explicitly incorporating intracranial haemorrhage into their model, Pink and colleagues captured the treatment specific rates of intracranial haemorrhage and the clinical consequences.

Although intracranial haemorrhage is the most important risk of any anticoagulant, other risks need to be considered. Dabigatran can also cause bleeding at other sites and dyspepsia. Pink and colleagues accounted for the cost and utility decrements of bleeds by modelling them explicitly: they estimate the cost of a major bleed as £1685 and the disability as 0.1385 for one 12th of a year—equivalent to about a 0.01 loss in QALY. For dyspepsia, they modelled the cost of treatment

8 Swedlow AI, Feychting M, Green AC, Kheifets L, Savitz DA; International Commission for Non-Ionizing Radiation Protection Standing Committee on Epidemiology. Mobile phones, brain tumours and the Interphone Study: where are we now? Environ Health Perspect 2011; published online; http://dx.doi.org/10.1289/ehp.1103693.
with a proton pump inhibitor but did not explicitly account for the transient utility decrement of dyspepsia. However, the effect of dabigatran induced dyspepsia on quality adjusted survival was much less than 0.01 QALY in another model— not enough to alter cost effectiveness significantly. Besides dyspepsia, RE-LEY initially reported an increased risk of myocardial infarction with dabigatran, but a reanalysis found that this trend was not statistically significant. Pink and colleagues chose to incorporate an increased risk of myocardial infarction into their model. Whether this inclusion improves accuracy depends on whether the lower rate of myocardial infarction with warfarin is a real effect, which seems likely. In summary, Pink and colleagues’ model incorporates the relevant health states needed to estimate cost effectiveness accurately.

To be valid, the decision model also needs to quantify risks, costs, and utilities accurately. When these parameters were compared with those from other studies (table), Pink and colleagues’ results were similar. Although the baseline stroke rate in Pink and colleagues’ study is slightly higher than in the comparator studies, all four studies examined a range of stroke rates and stratified their results appropriately.

These studies found that dabigatran was likely to be cost effective for patients at high risk of stroke (CHADS\(^2\), score of 3 or more), unless international normalised ratio (INR) control was excellent. For example, at a CHADS\(^2\), score of 3, Pink and colleagues calculated a cost of £15 895 per QALY for centres with average INR control. In contrast, all studies found that the cost per QALY gained was high in patients at low risk of stroke.

In practice, clinicians should consider additional factors when choosing treatment, such as patient preference and adherence. For patients with a strong aversion to INR monitoring, dabigatran will be more cost effective than warfarin. In contrast, for patients with poor adherence to treatment, dabigatran will be less cost effective because it has a shorter half life than warfarin.
The RTS,S vaccine illustrates two general points about the next generation of vaccines against several major diseases. It is not realistic to expect the first generation of new vaccines against diseases such as malaria, tuberculosis, and HIV—where complete immunity is difficult to acquire from natural infection—to have similar efficacy to those against rubella or measles—where natural disease induces lifelong protection. Partially effective vaccines are, where cost effective, a great deal better than no vaccine and should be celebrated as such. Over-hyping them runs the serious risk that people will paradoxically be disappointed by (the good) reality. Loose talk sometimes heard at scientific conferences that “no disease has ever been eradicated except with a vaccine” is strictly true, because only two diseases have so far been eradicated (smallpox and rinderpest), but it feeds the public perception that vaccines are somehow uniquely powerful tools. The next disease to be eradicated may well be guinea worm, and no vaccine has played a part in this.

These partially effective vaccines will also be just one of a range of control tools against their target disease, and they will be judged for the cost effectiveness of the additional benefits they bring as part of a combination of measures. With smallpox there was only one tool—a highly effective vaccine. It was the silver bullet. For polio or measles, vaccines are somewhat cheaper and have some role. The challenge is figuring out what that role will be.

8. GS gives price pledge on malaria vaccine. Financial Times 2010. www.ft.com/cms/s/0/3fbbdda4-05f1-11df-a97f-90144feadb0d.html#axzz1bdRcjCBW.
control, local and distant recurrence, new tumour formation, and overall survival. The recently published update of these trials on long term outcomes (median 207 months for the B-17 trial and 163 months for the B-24 trial) extends knowledge about the usefulness and relative importance of adding radiotherapy to segmental excision, and about the further addition of tamoxifen to treatment with lumpectomy and radiation.4

Four randomised controlled trials have shown the benefit of adjuvant whole breast radiotherapy in the breast conserving treatment of DCIS. An overview of these trials reported that adjuvant whole breast radiotherapy reduces the risk of locally recurrent DCIS and invasive local recurrence by about 50%, and the effect is similar for all clinical and histological subgroups.5,7 However, the risk of recurrence of DCIS varies—for example, a higher risk is associated with younger age at diagnosis and the presence of involved margins at surgery. In these subgroups, even with radiotherapy, the observed local recurrence rates are more than 20% at 10 years, which is considerably higher than local recurrence rates after breast conserving treatment for invasive disease.8 Some subtypes could possibly be treated with less total radiation, but the optimal radiotherapy dose has yet to be established. Also, some patients with DCIS will probably have such a low risk of recurrence that radiotherapy could be safely omitted, but they have yet to be defined.

Overall, the trials show that tamoxifen exerts an additional protective effect when combined with local breast conserving surgery and radiotherapy. In the NSABP B-24 trial, 1804 women were randomised (1:1) to treatment with lumpectomy plus radiation, with or without tamoxifen. Overall, tamoxifen reduced the risk of recurrent events by nearly 40%, with a hazard ratio of 0.63.3 However, earlier results from the NSABP studies of tamoxifen in women with resected DCIS showed no improvement in overall or cancer specific survival.9,10

The recent update of the NSABP trials confirms the general principles above and provides a more specific estimate of the risk. Radiotherapy reduced the recurrence of invasive ipsilateral breast tumours by 52% in women treated with lumpectomy plus radiotherapy compared with those treated with lumpectomy alone (absolute risk 19.6% in the lumpectomy alone group v 10.7% in the lumpectomy plus radiotherapy group; hazard ratio 0.48, 0.33 to 0.69, P <0.001). The addition of tamoxifen to the group that received lumpectomy and radiotherapy reduced the risk of invasive ipsilateral breast cancer by a further 32% (absolute risk 9% without the addition of tamoxifen v 6.6% with the addition of tamoxifen; 0.68, 0.49 to 0.95, P=0.025).

In earlier 2000 and 2003 updates of these trials, 8.2% of women in the tamoxifen group developed cancer over five years compared with 13.4% in the group not treated with tamoxifen (P=0.0009). The 15 year cumulative incidence of recurrence of invasive ipsilateral breast cancer was 19.4% in the lumpectomy alone group, 8.9% in the group treated with lumpectomy and radiation, and 8.5% in the group treated with tamoxifen after lumpectomy and radiotherapy. This same analysis for development of contralateral tumours was 10.3%, 10.2%, and 7.3%, respectively. Of importance, the development of invasive ipsilateral recurrences was associated with increased mortality, although recurrence of DCIS was not. The 15 year cumulative incidence of death from breast cancer was significantly lower in the group treated with tamoxifen after lumpectomy and radiotherapy (2.3%), compared with the group treated with lumpectomy alone (3.1%), or the group treated with lumpectomy and radiation (4.7%). The incidence in the group treated with lumpectomy, radiation, and placebo was 2.7%. This analysis highlights some of the difficulties of evaluating the subsets even in large and long term studies.

These cumulative indices refer to all patients, with or without recurrence of invasive ipsilateral breast tumours. DCIS comprises a group of heterogeneous diseases, which are characterised partly by the fact that it is impossible to distinguish how aggressive and subclinically invasive the tumours are, and partly by the lack of molecular markers that can identify non-invasive tumours that can subsequently become invasive.

Genome and candidate gene studies have analysed molecular profiles of DCIS to determine which molecular markers can predict the risk of recurrence of invasive cancer.11 They have shown the molecular heterogeneity that has been suspected from clinical observations, but the gene signature needed to predict and isolate those cases that will progress or result in invasive disease has not been identified. Such molecular analyses and biological profiling provide the opportunity to increase our understanding of tumour biology and tailor treatment to the specific disease subtype. The result should enable tailored treatment to be given only to those women who would benefit.