recommendation of developing quantitative measures of drug-induced harm and benchmarks for its recommended behavioural treatments, it does not take a similar approach to this necessary training proposal.

The report is unclear about where the newly trained researchers will be deployed. Clinically approved drugs for substance abusers developed in academic settings have failed in multicentre trials for veterans in community settings.[4,5] A lack of generalisable studies in academic settings underscores the need for some academic researchers to do studies in community settings rather than in academic clinics. There will need to be safeguards against adopting the non-academic benchmarks used in large hospitals, such as scope of clinical practice. Whereas in academia a major benchmark is the number and influence of publications, in hospitals the amount of clinical funding alone is often the major benchmark. We must be cautious that academic physicians are held to publication-based standards as opposed to gauging success merely by their ability to procure funding.

But publication alone, while important for academic promotion, may not be sufficient to jump-start translational drug-development. Since the report was written, several double-blind studies have shown that cognitive enhancers promote behavioural treatment of social anxiety and obsessive-compulsive disorders.[6–8] Although these results are promising, they frustrate the clinician. The findings are either insufficient to alter clinical practice or, as is often the case after small phase II academic trials, to satisfy sceptical reviewers.[9] Clearly, industry needs to play the important role in filling this void between promising small academic phase II studies and larger phase III trials. That is why the recommendation of the Academy's report to adopt a flexible approach to drug pricing—taking account of the overall societal value of such drugs—is important. Orphan drug legislation in the USA has been uniquely successful in spurring industry to quickly develop old drugs for new uses, because time-consuming studies to establish safety have long since been completed. The sheer size of this success, by the type of academic clinical researcher that the report advocates training, begs the question: what if this approach to intellectual property, which (like the report's recommendation) takes into account overall societal value, were extended to using old drugs for more common conditions. If policy makers embrace this report's recommendation to expand the number of translational professionals and modernise antiquated intellectual property law.[10] there is hope for at least doubling the rate of drug development.

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Metabolically healthy but obese individuals

A subset of obese individuals seems to be protected against obesity-related metabolic complications.[1,2] These individuals are described as metabolically healthy but obese, or as having uncomplicated obesity,[3] or metabolically benign obesity.[4] Despite having excessive body fat, people who are metabolically healthy but obese have favourable metabolic profiles, characterised by remarkably high insulin sensitivity, no sign of hypertension, and normal lipid, inflammation, and hormonal profiles (low triglycerides and C-reactive protein concentrations and high HDL cholesterol and adiponectin concentrations).[5–7]

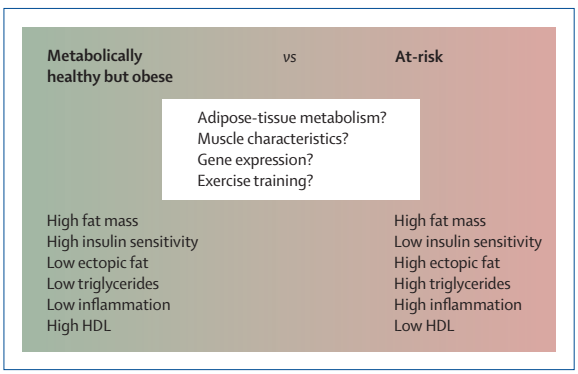

Figure: **Factors that might distinguish metabolically healthy but obese individuals from at-risk obese individuals**

The metabolic profiles of metabolically healthy but obese individuals are almost indistinguishable from those of young lean individuals.[8] Furthermore, a longitudinal study reported that the protective metabolic profile of these individuals was associated with low incidences of type 2 diabetes and cardiovascular diseases.[9]

Up to 30% of obese people seem to be metabolically healthy,[1] and a recent study of US adults 20 years and older reported that 31·7% of obese adults (about 19·5 million people) were metabolically healthy.[10] However, metabolically benign obesity is not without risk. Obesity is associated with other non-metabolic complications (eg, osteoarthritis and obstructive sleep apnoea). Despite general clinical awareness of metabolically benign obesity, there is only a rudimentary understanding of the factors underlying this protective profile.

A recent study by Norbert Stefan and colleagues[4] confirmed the existence of metabolically healthy but obese people and added new information about possible mechanisms that could explain the protective metabolic profile. People with metabolically benign obesity had lower visceral, liver, and muscle fat content than did insulin-resistant obese people. This finding suggests that metabolically healthy but obese people have a better ability to trap free fatty acids in adipose tissue. Additionally, these people had lower intima–media thickness in the carotid artery, which suggests a favourable cardiovascular profile.

There are no standardised criteria to categorise metabolically healthy but obese individuals, except for the presence of obesity (body-mass index ≥30 kg/m^2). The following methods have been used to identify such individuals: the hyperinsulinaemic–euglycaemic clamp (infusion of glucose >8 mg min^{-1} kg^{-1} of lean body mass,[6] upper quartile of glucose disposal rates);[7] the upper quartile of an insulin sensitivity index derived from oral glucose-tolerance tests;[4] fewer than two cardiometabolic abnormalities (systolic/diastolic ≥130/85 mm Hg, triglycerides ≥1·7 mmol/L, glucose ≥5·6 mmol/L, homoeostasis model assessment [HOMA] >5·13, high-sensitivity C-reactive protein >0·1 mg/L, HDL <1·3 mmol/L);[10] and meeting four of five metabolic factors (HOMA ≤2·7, triglycerides ≤1·7 mmol/L, HDL ≥1·3 mmol/L, LDL ≤2·6 mmol/L, high-sensitivity C-reactive protein ≤3·0 mg/L).[11] Despite the differences in the methods used to distinguish between metabolically healthy but obese and at-risk obese people, we observe some recurrent characteristics, such as a favourable lipid profile and lower visceral fat content.

An important question that seems to be unresolved is whether metabolically healthy but obese individuals would gain any metabolic benefit from dietary or exercise intervention.[12] Would an attempt to achieve weight loss in such individuals, by diet or exercise, be harmful given the favourable metabolic profile? Recently, my colleagues and I suggested that metabolically healthy but obese individuals responded differently to a 6-month restricted caloric diet compared with at-risk obese people achieving similar weight loss.[13] Insulin sensitivity improved by about 26% in at-risk individuals but deteriorated by about 13% in metabolically healthy but obese individuals.[13] Future studies are needed to investigate the effect of exercise training on the metabolic profile of metabolically healthy but obese people.

Future investigation might examine the roles of gene expression, transport of free fatty acid, storage and utilisation, and skeletal-muscle insulin-signalling pathways in metabolically healthy but obese individuals (figure). Such investigations might improve our understanding of the pathophysiology of the protective metabolic characteristics, which could lead to a better understanding of the mechanisms of insulin resistance, the causes of type 2 diabetes, and potential mechanistic links between diseases (eg, cardiovascular disease) and obesity.

A better understanding of metabolically benign obesity has important implications for medical education and clinical research. Education of health-care professionals

and physicians about the different needs of subsets of obese individuals is important. The tendency to treat obese individuals with a one-size-fits-all approach will be counterproductive with metabolically healthy but obese people. And in clinical research, data from cohorts mixing at-risk individuals with those with metabolically benign obesity might be difficult to interpret.

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Collapse of GMC hearing into research misconduct

On July 4, the UK's General Medical Council (GMC) announced that their Professional Conduct Committee had halted a disciplinary hearing into a research study done in Stoke on Trent, Staffordshire, UK, between 1990 and 1993.[1] The study, the CNEP trial, was designed to compare two strategies for supporting the breathing of preterm babies.[2,3] A complaint about this study had been lodged with the GMC in April, 1997, but a public hearing finally opened only in May, 2008. The main allegations were of failure to obtain informed consent, misleading the research ethics committee, faulty trial design and analysis, and misleading presentation of results.

The GMC put the testimony of three experts before the Panel on behalf of the complainants. Two could find little to fault in the conduct of the study, and the Panel had considerable reservations about whether the third qualified as an expert because he had "little or no formal training in medical ethics" and was no longer on the medical register.[1] The Panel went on: "Furthermore, he has until recently published articles in his Bulletin of Medical Ethics and been quoted in the media such as to demonstrate a deep animosity towards Dr David Southall".[1] The ruling continued: "The Panel does not think that any reasonable Panel could safely rely on his opinion evidence." Hey[4] has already written, in 2006, that the allegations of consent forms being fabricated were highly implausible. The Panel observed that "given the lapse of time, it could not be proved to the required standard that consent was not taken properly".[1] They dismissed the case against the three doctors after listening to four barristers and 27 witnesses over a period of 8 weeks without even asking to hear what the defence had to say.

The GMC's first task is to protect the public, but the public will not think much of the protection on offer if review sometimes takes 11 years. It has been a costly as well as a lengthy business. The Department of Health will not reveal the cost of the inquiry they commissioned, or admit to its flaws.[5] Had they done so, the issues before the GMC would certainly have been settled much sooner. The local hospital Trust spent the best part of £1 million dealing with the complaint.[6] The medical defence societies have spent a similar sum in the past 10 years, and the GMC must have spent a substantial sum preparing its case, appearing in the High Court and the Court of Appeal, and holding its own hearings.