Open letter to UK Prime Minister David Cameron and Health Secretary Andrew Lansley on safety of medicines

We are writing to you as a group of clinicians and scientists to express our concern about the escalating problems of drug failures and adverse drug reactions. The UK pharmaceutical industry is in crisis, as the departure of Pfizer from the Sandwich site makes plain. Likewise, health care is in a web of crises, many of which are intimately linked to the pharmaceutical industry's major problems.

Adverse drug reactions have reached epidemic proportions and are increasing at twice the rate of prescriptions.[1] The European Commission estimated in 2008 that adverse reactions kill 197 000 EU citizens annually, at a cost of €79 billion.[2] The cost of new medicines is rising unsustainably, creating an ever-increasing burden on the National Health Service (NHS). Meanwhile, many increasingly prevalent diseases, such as Alzheimer's disease, diabetes, many cancers, and stroke, remain without adequate treatments.

The major reason for the rising cost of new drugs is the fact that more than 90% of them fail in clinical trials.[3] Companies need to recoup the cost of development not only for the drug that succeeds, but for the nine others that fall by the wayside.

It is increasingly clear that an important factor contributing to these problems is the over-reliance of the pharmaceutical industry on the use of animals to predict drug behaviour in man. The stark differences, not only in the diseases of different animal species, but also the ways that they respond to drugs, are now well known. Many studies have shown that animal tests frequently fail to translate to the clinic, with estimates of their ability to predict effects on people as low as 37–50%, or no better than the toss of a coin.[4]

Our reliance on animals to establish safety results in the exposure of clinical volunteers and patients to many treatments that are at best ineffective and at worst dangerous. Take for example the notorious Northwick Park clinical trial drug, TGN1412, that left six young men in intensive care in 2006. This drug was demonstrably safe in monkeys at doses 500 times higher than those that nearly proved fatal to the volunteers.[5] Soon after the disastrous trial, an assay that used human cells was developed to predict such an immune system over-reaction.[5] Had this assay been in use before human beings were exposed, the trial would never have taken place. Surely the time has come for there to be a rigorous assessment of the ability of such human-based tests to improve on the deeply flawed, animal-based approaches in current use?

We call on the UK Government to initiate a comparison of a set of human-biology-based tests with those currently used, as proposed in the Safety of Medicines Bill 2010–11,[6] to see which are more effective for predicting the safety of medicines for patients. Several new technologies promise increased clinical predictability as well as substantial improvements in efficiency and cost. The Bill does not propose any replacement of animal tests, merely their assessment of fitness for purpose. 148 Members of Parliament have already signed a motion[7] in support of this proposal.

Some of us recently made representations to the UK Department of Health, and were told that the Government believes that human-biology-based systems have not been established as being more predictive than are animal studies for developing safer medicines. We agree, but that is because no rigorous examination of such systems has been undertaken. The very purpose of the proposed comparison is to initiate such an examination, which is urgently necessary for the sake of the NHS, the pharmaceutical industry, and, most importantly, patients.

We urge you to act now to ensure that the best technologies currently available are used to establish the safety of medicines for patients.

We declare that we have no conflicts of interest.

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For a full list of signatories, see **Online** for webappendix

Global trends in body-mass index

In a comprehensive assessment of trends in body-mass index (BMI) in 199 countries, Mariel Finucane and colleagues (Feb 12, p 557)[1] show that mean BMI and prevalence of overweight have increased since 1980, concluding that "interventions and policies that can curb or reverse the increase…are needed in most countries". Caution, however, is warranted in interpreting the country-specific or region-specific

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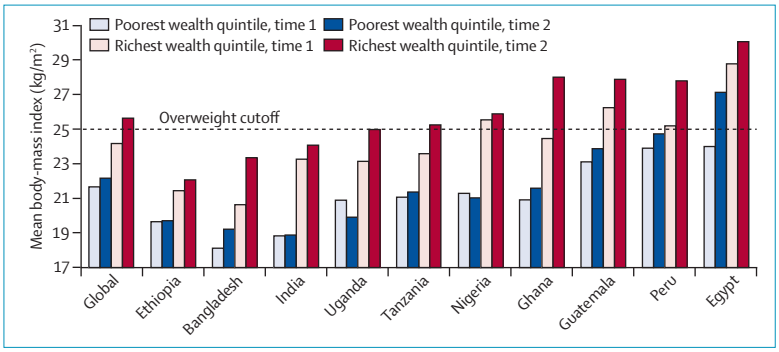

Figure: **Global and country-specific trends in mean body-mass index for ever-married women from the poorest and richest quintiles of household wealth**
Data are from the Demographic and Health Surveys, which are administered by ICF Macro (Calverton, MD, USA). Surveys are repeated cross-sections, and are nationally representative in each time period. Countries selected for this example are those that have at least two surveys and have the height/weight module and wealth index information. Owing to space constraints only ten countries are shown here. For a figure showing all the 37 eligible countries and the underlying data, see webappendix.

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average trends, especially in low-to-middle-income countries.

The most recent, nationally representative data on adult women from 54 low-to-middle-income countries, with objectively measured BMI, unequivocally show a positive association between BMI or overweight and socioeconomic status in 52 countries.[2] In a subsample of 37 countries with several surveys over time, increases in BMI and overweight prevalence seem to persist in groups with high socioeconomic status in most countries (figure). Even though increasing BMI is no longer confined to high-income countries, it remains concentrated among high-income people within low-to-middle-income countries.

Although Finucane and colleagues mention their lack of consideration of differences in socioeconomic status within countries as a limitation, presentation of average trends alone is problematic from a policy perspective. Indeed, the positive association between socioeconomic status and BMI in low-to-middle-income countries raises a provocative question: should precious public resources be targeted to reducing overweight among the rich or should they be devoted to policies that improve nutritional outcomes among the poor?

The global epidemic of cardiovascular risk factors, thus far, remains concentrated in the high socioeconomic status groups—a fact missed in the study by Finucane and colleagues, and overlooked in the published studies on cardiovascular risk factors in low-to-middle-income countries, as shown elsewhere.[3,4] Soaring food prices, combined with increasing income inequality spurred by polarised economic growth in low-to-middle-income countries,[5] suggest that this trend might not alter very soon. In short, public health policies to address cardiovascular disease burden can be seriously misleading, and potentially unfair, without an explicit consideration of the social distribution of the burden.

We declare that we have no conflicts of interest.

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Mariel Finucane and colleagues[1] used population-representative data on measured weight and height from 199 countries and territories to estimate national, regional, and worldwide trends in body-mass index (BMI) in adult men and women from 1980 to 2008. They found an increase in mean BMI in all regions worldwide; in 2008, an estimated 1·46 billion adults were overweight (BMI ≥25 kg/m²), including 500 million who were obese (BMI ≥30 kg/m²). Estimated prevalences for higher BMI categories, however, were not reported.

Although the risks of disease and premature death increase progressively with BMI,[2] few reliable data exist for population-based trends in extreme BMI ranges (eg, BMI ≥40 kg/m² and BMI ≥50 kg/m²) owing to the large sample sizes required. Telephone survey data from the USA suggest that the prevalence of adults with extreme BMIs has increased several times faster than have the prevalences of overweight and moderate obesity.[3] Population distributions of BMI do not follow a bell-shaped form but are right-skewed, particularly in women.[4] In a study of 4776 people who had had bariatric surgery, in which 33% had a BMI of 50 kg/m² or more, 3767 (79%) were women.[5]

A disproportionately rapid increase in the prevalence of extreme BMI highlights the need to prevent obesity in the general population and to enable health-care services to tackle increasing numbers of patients with severe obesity. Finucane and colleagues could use their unique dataset[1] to assess sex-specific trends for higher BMI categories on national, regional, and global levels.

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