The balance of safety and efficacy in today’s study is encouraging, but it is impossible to draw definitive clinical conclusions from such a phase II study. Experience with muraglitazar has shown that a good lipid and blood glucose profile is not sufficient to predict clinical outcomes. It is a strength that cardiovascular events, including heart failure, were adjudicated in SYNCHRONY (two cases of heart failure, no myocardial infarctions), but the sample size and short duration of the study do not allow firm conclusions.

Diabetes is a complex disease and agents of the PPAR class could be promising owing to the multiple effects of these drugs and the development of selective PPAR modulators, but long-term safety is a major concern. Research in this difficult area must be encouraged, and the coming years will tell whether hopes raised by the SYNCHRONY study for aleglitazar are confirmed by appropriate long-term clinical trials.

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Reporting genetic association studies: the STREGA statement

The completion of sequencing of the human genome created high hopes for the translational potential of knowledge from genetic association studies. The combination of advances in genomic and related technologies and methods of conventional epidemiology has produced one of the most dynamic fields of medical research. Genome-wide association studies have led to an unparalleled growth and improved accuracy in genetic information. At the same time, the complexity of the available data has increased substantially. However, advances in the application of this knowledge, such as determination of an individual’s risk of disease or development of personalised therapies, might not become available as quickly as expected. The devil is in the detail. For instance, for the suggested relation between several genetic polymorphisms and occurrence of sepsis in human beings, systematic review in 2006 of the study reports showed that the information needed to assess the risk of bias was lacking.

Results of medical research need to be reported with sufficient accuracy and transparency to enable critical appraisal. Reporting guidelines aim to improve the research literature by the use of checklists with items deemed essential by multidisciplinary working groups. The STrengthening the Reporting of OBServational Studies in Epidemiology (STROBE) statement was developed to help authors to improve the reporting
Rationale for inclusion

<table>
<thead>
<tr>
<th>Genotyping errors</th>
<th>Non-differential genotyping errors will usually bias associations towards the null; when there are systematic differences in genotyping according to outcome status (differential error) bias in any direction can occur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population stratification</td>
<td>This type of confounding can occur if study subpopulations differ both in allele (or genotype) frequencies and disease risks, and if these subpopulations are unevenly distributed across exposure groups (or between cases and controls)</td>
</tr>
<tr>
<td>Modelling haplotype variation</td>
<td>In studies with a design covered by STREGA, haplotypes have to be inferred because of absence of available family information; because there are diverse methods for inferring haplotypes, they should be reported</td>
</tr>
<tr>
<td>Hardy-Weinberg equilibrium</td>
<td>Departure from HWE might suggest errors or peculiarities in the data; reports of genetic associations do not always include information about conformity with HWE and some have limitations or errors in HWE assessment</td>
</tr>
<tr>
<td>Replication</td>
<td>Publications that present and synthesise data from several studies in a single report are becoming more common; in particular, many genome-wide association analyses describe several study populations, sometimes with different study designs and genotyping platforms, and in various stages of discovery and replication</td>
</tr>
<tr>
<td>Selection of participants</td>
<td>Selection bias can occur if genetic associations are investigated in one or more subsets of participants (subsamples) from a particular study, if there is differential non-participation in groups being compared, or if there are differential genotyping call rates in groups being compared</td>
</tr>
<tr>
<td>Rationale for choice of genes and variants selected</td>
<td>Without an explicit rationale, potential for selective reporting of study results is difficult to judge; empirical evidence exists for other types of studies (eg, randomised trials) that the reporting of outcomes is frequently incomplete and biased in favour of statistically significant findings</td>
</tr>
<tr>
<td>Treatment effects in studying quantitative traits</td>
<td>Study of a quantitative variable can be compromised when the trait is subjected to effects of treatment (eg, lipid-related trait for which several individuals are taking lipid-lowering drugs); without appropriate correction, this effect can lead to bias in effect estimates and loss of power</td>
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<tr>
<td>Statistical methods</td>
<td>Analysis methods should be transparent and replicable; genetic association studies are often done with specialised software, which should be reported</td>
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<tr>
<td>Relatedness of participants</td>
<td>Methods of analysis used in family-based studies are different from those used in studies based on unrelated cases and controls; even in studies based on apparently unrelated individuals, some might be (distant) relatives; this possibility might need to be probed with appropriate methods and adjusted for in data analysis</td>
</tr>
<tr>
<td>Reporting of descriptive and outcome data</td>
<td>Synthesis of findings across published studies depends on availability of sufficiently detailed data from the individual studies</td>
</tr>
<tr>
<td>Issues of data volume</td>
<td>Key problem is of possible selective reporting of false-positive results; type I errors are especially relevant in genome-wide association studies because large searches among genetic variants can be expected to find positive results with odds ratios significantly different from 1 by chance alone</td>
</tr>
</tbody>
</table>

STREGA=STrengthening the REporting of Genetic Association studies. HWE=Hardy-Weinberg equilibrium.

Table: Rationale for areas covered by STREGA items that are specific to genetic association studies

of cross-sectional, case-control, and cohort studies. Genetic association studies that use one of these study designs present several specific challenges. As part of its road map for human-genome epidemiology, the Human Genome Epidemiology Network set up a working group to provide guidance on how to report these studies. This initiative, called STrengthening the REporting of Genetic Association studies (STREGA), elaborated on the STROBE statement. The resulting STREGA statement was recently published in several journals simultaneously. The STREGA checklist provides additions to 12 of the 22 items of the STROBE checklist to cover crucial aspects of genetic epidemiology reporting (table). Each of these areas has a rationale given.

In the fast-moving field of genetic association studies, the risk of new methodological pitfalls is high. The effects of individual variants in common disorders are almost always modest. Generally, the credibility of gene–disease associations is low if the evidence comes from single studies of small scale and cannot be replicated. Genetic evidence can only transform the prevention, diagnosis, or therapy of diseases if it is consistent and strong. The STREGA statement is neither prescriptive, nor does it pass judgment on how researchers have done their studies. Rather, the statement advocates for transparency in reporting how a study was done. This transparency might help to inform the design, conduct, and analysis of future studies, and improve the reliable integration of evidence from multiple studies. STREGA can help authors to include the essential information in reports of both smaller association studies and large-scale analyses of data from several sources. Earlier reporting guidelines, such as the CONSORT statement, have also proven useful for peer reviewers and editors. Evidence emerges that they also helped to improve the quality of research reports. The endorsement by journals—eg, in instructions for authors or reviewers—will be key to the success of the STREGA statement and of other reporting guidelines. If, on top of enhanced accuracy and transparency, the STREGA recommendations can help to make articles on genetic association studies an easier read for both specialised and less proficient readers, it will have served its purpose.

*Erik von Elm, David Moher, Julian Little, on behalf of the STREGA collaboration*
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We thank France Gagnon, Julian Higgins, John Ioannidis, and Muin Khoury for helpful comments. We are co-authors of the STREGA statement and are involved in other reporting guideline initiatives, including CONSORT, STROBE, and the EQUATOR Network. Maja Zeecevic, North American Senior Editor at The Lancet, was part of the STREGA group.


New WHO growth standards: roll-out needs more resources

On May 22, WHO and UNICEF issued a statement endorsing new case definitions of severe acute malnutrition based on the 2006 WHO growth standards.1 Before the global food crisis, a 2006 review estimated that 13 million children had such malnutrition.2 By January, 2009, aid agencies reported about 19 million affected.3 Calls were made for the disease-burden demand to be met with increased supply of treatment services.4 Increases in the prevalence of severe acute malnutrition associated with adoption of the new case definitions have been noted,4 but balances in treatment–service supply and demand are also crucial and need to be urgently addressed.

Numbers of children diagnosed as malnourished vary greatly depending on which case definition is used. Each has advantages and disadvantages, and is useful for particular purposes. Malnutrition for admission to feeding programmes was originally defined by low weight-for-age.5 This definition was changed to weight-for-height6 to better identify children who would benefit most from treatment. Weight-for-height expressed as Z scores is useful for surveys, yet many treatment programmes admit children with conceptually simpler %-of-median measures. (Minus Z scores below the WHO standard describing how children should grow when measured by weight and height.7 Increases in the diagnoses of severe acute malnutrition associated with adoption of the expected change in prevalence estimates for severe acute malnutrition.) More recently, focus has been on mid-upper-arm circumference.7

WHO growth standards are an international gold standard describing how children should grow when measured by weight and height.7 Previously, severe acute malnutrition was defined as weight-for-height <70% or <-3 Z scores below the National Centre for Health Statistics (NCHS) median. The new case definition is weight-for-height <-3 Z scores below the WHO growth standards median. The diagnostic threshold of mid-upper-arm circumference has also been changed from 110 mm to 115 mm. Increases in the diagnoses of severe acute malnutrition with the new WHO weight-for-height criteria have been noted.8,9 However, until now there has been no documentation of which case definition countries are using, and therefore the size of the expected change in prevalence estimates for severe acute malnutrition.

In the table, we present treatment admission criteria in 22 countries where severe acute malnutrition is

<table>
<thead>
<tr>
<th>Table: Case definitions of severe acute malnutrition in 22 national guidelines</th>
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<tr>
<td>Number of cases</td>
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<tr>
<td>&lt;70% of median weight-for-height (NCHS)</td>
</tr>
<tr>
<td>&lt;70% of median weight-for-height (NCHS), or &lt;3 weight-for-height Z scores (NCHS)</td>
</tr>
<tr>
<td>&lt;-3 weight-for-height Z scores (WHO)</td>
</tr>
</tbody>
</table>

Asia, 4; Eastern Africa, 8; Middle Africa, 1; Northern Africa, 2; Western Africa, 6; Southern Africa, 1. Guidelines include versions marked as final or draft. All protocols classify oedematous malnutrition as severe acute malnutrition, and all accept mid-upper-arm circumference <110 mm as defining such malnutrition.