

Within each household, the children formed several full-sibling, half-sibling, and first-cousin groups. The second study monitored severe malaria that led to hospitalization and nonmalaria hospitalizations in 2,900 children, also over a five-year period. This analysis concentrated on full-siblings.

Using a standard statistical genetics method of relating similarity in phenotype to similarity in genotype, they found that host genetic factors accounted for approximately one-quarter to one-third of the total variation in susceptibility in the populations to malaria. Of this percentage, only a small proportion could be attributed to the best known malaria resistance genes. This is consistent with other studies that suggest that malaria susceptibility is under the control of many different genes, with each individual gene having a relatively small epidemiological effect.

When assessing the contribution of household factors, the researchers found that for mild clinical malaria, those factors accounted for slightly more than a quarter of the total variation. For hospitalized malaria, they contributed about 15%, and for hospitalizations with fever that turned out not to be malaria, they contributed approximately 35%. Overall, children living in the 10% of households with the highest malaria incidence had approximately twice as many infections per year than those living in the 10% of households with the lowest incidence.

The researchers do not question the long-term benefits of understanding the genetic factors but conclude that “identifying and tackling the household effects must be the more efficient route to reducing the burden of disease in malaria-endemic areas.” Factors such as suitable conditions for mosquitoes to breed and survive as well as human behavior are likely to play major roles. “We need to determine what makes the difference between low-risk and high-risk households,” Mackinnon says, “but whatever it is, it seems likely to be an easy target using tools such as education and the low-cost, low-tech devices that we already have at hand such as bed nets, residual indoor spraying, and cleaning up backyards for mosquito breeding sites.”

**Mackinnon MJ, Mwangi TW, Snow RW, Marsh K, Williams TN (2005) Heritability of malaria in Africa. DOI: 10.1371/journal.pmed.0020340**

## Bias in Reporting of Genetic Association Studies

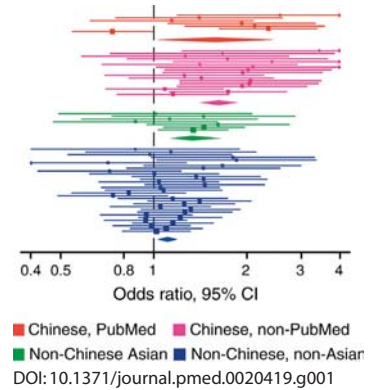
DOI: 10.1371/journal.pmed.0020419

One of the tools in the scientist's armory for resolving a medical issue or consolidating a body of clinical trials is the systematic review of the published medical literature. This technique involves doing a literature search and critical appraisal of individual studies, and in addition, may also use statistical techniques to combine the results of these studies. One of the aims of such reviews is to assess and then, ideally, include all appropriate studies that address the question of the review. But finding all studies is not always possible, and researchers have no way of knowing what they have missed. But does it matter if some studies are left out?

It would definitely matter if the missing studies differed significantly from the included ones. And the worst-case scenario is that the accumulation of evidence might point to the wrong answer if the studies included are unrepresentative of all those that have been done.

Studies of publication bias have noted that papers with significant positive results are easier to find than those with nonsignificant or negative results. As a result, overrepresentation of positive studies in systematic reviews might mean that such reviews are biased toward a positive result. Publication bias is just one in a group of related biases, all of which potentially lead to overrepresentation of significant or positive studies in systematic reviews. Other types of bias include time lag bias (positive studies are more likely to be published rapidly); multiple publication bias (positive studies are more likely to be published more than once); citation bias (positive studies are more likely to be cited by others); and language bias (positive studies are more likely to be published in English).

In *PLoS Medicine*, John Ioannidis and colleagues have taken a closer look at bias in Chinese genetics studies. Research done in non-English-speaking countries has two outlets. A study might be published in English-language journals, which are usually indexed in major international bibliographic databases such as PubMed, or in domestic journals, many of which are not indexed in international databases. The Chinese literature is a prominent example of where domestic scientific journals are not catalogued in international databases. There is some



### Different results in local literature studies

evidence that the decision to publish in international versus domestic journals might be influenced by the results. For example, significant results are often published in international journals, whereas nonsignificant results appear in the local literature, resulting in a language bias—although, the reverse situation has also been described.

Genetics studies pose particular problems for impartial reporting. There are millions of polymorphisms in the human genome, and an exponentially increasing number of studies are trying to associate genetic polymorphisms with risk of disease or treatment outcomes. Selective publication might invalidate the overall picture of genetic risk factors.

The authors examined 13 gene–disease associations. Studies were more likely to be published when the disease was considered common in China. They found 161 Chinese studies on 12 of these gene–disease associations, only 20 of which were indexed in PubMed. Chinese studies had significantly more prominent genetic effects than non-Chinese studies, and 48% were statistically significant per se, despite their smaller sample size. Moreover, the largest, most exaggerated genetic effects were often seen in PubMed-indexed Chinese studies. Chinese studies usually appeared several years after their equivalent was first postulated in the world literature.

The larger genetic effects in Chinese studies are unlikely to reflect genuine heterogeneity and are more likely to do with publication bias operating within the Chinese literature, say the authors. It is possible that there was reluctance to submit and publish negative or inconclusive results when a large body

of English-language literature has shown the presence of genetic effects. However, such “forced” confirmation negates the importance of independent confirmation of research results. This problem is probably not limited to the Chinese literature. These phenomena haven’t been noted in molecular medicine before, but could become a serious problem in such a fast-moving field. Moreover, the inclusion of poor-quality research and additional selectively reported data may contaminate the better literature rather than provide a more accurate, comprehensive picture.

The findings have two broad implications. First, language bias might be important to consider in meta-analyses of observational studies, where its effect might be larger than its effect on randomized evidence. Second, because human genome epidemiology is a global enterprise, a comprehensive global view is important to help decipher artifacts from true genetic effects. The Chinese literature in particular will be essential for the evaluation of evidence on genetic risk factors. China is making rapid scientific progress in this field and

joining in international collaborative projects, such as the Human Genome Project. To develop a global perspective, one way forward might be for all investigators working on the genetics of a specific disease to register with a common network, making it easier to trace additional unpublished or nonindexed data.

**Pan Z, Trikalinos TA, Kavvoura FK, Lau J, Ioannidis JPA (2005) Local literature bias in genetic epidemiology: An empirical evaluation of the Chinese literature. DOI: 10.1371/journal.pmed.0020334**

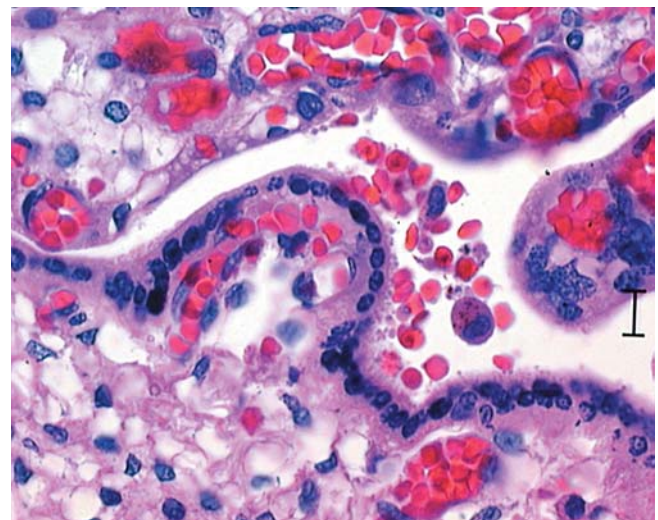
## Surprising Effects of Maternal Malaria and Gravidity on Infant Malaria Burden

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Every year at least 30 million women in malarious areas of Africa become pregnant. The symptoms and complications of malaria during pregnancy differ with the intensity of malaria transmission and with the level of immunity acquired by the pregnant woman. In areas where malaria is endemic, most adult women have developed sufficient immunity such that, even during pregnancy, *P. falciparum* infection does not usually result in fever or other clinical symptoms. In these areas, the principal impact of malaria infection is due to the presence of parasites in the placenta. Placental malaria frequently results in low birth weight, and estimates suggest that in endemic areas 19% of cases of infant low birth weight are due to malaria, and that 6% of infant deaths are due to low birth weight caused by malaria.

In addition to affecting birth weight, placental malaria might increase the susceptibility of infants to malaria, but so far studies on this subject have been inconclusive. Patrick Duffy and colleagues examined the effect of placental malaria on infant malaria susceptibility in a prospective cohort study of newborns in a malaria-endemic area. They monitored parasitemia in 453 infants in a region of northeastern Tanzania where malaria transmission is very high (with an estimated 400 infective mosquito bites per individual per year). Sixty-nine of the infants were born to mothers with placental malaria. Placental malaria is caused by a different form of the malaria parasite, which does not commonly infect nonpregnant individuals. Even in endemic areas, women, therefore, lack immunity to the placenta-specific form of the parasite prior to their first pregnancy, but acquire it over successive pregnancies. As a consequence, placental malaria is most frequent and severe in first-time mothers. Of the 69 mothers with placental malaria in this study, 45% were first-time mothers (or primigravid), 38% were giving birth to their second child (secundigravid), and 17% had had multiple prior pregnancies (multigravid).

Overall, infants of mothers with placental malaria were 41% more likely to experience malaria parasitemia themselves in the first year of life. However, the odds of parasitemia throughout infancy were also strongly influenced by the mother’s gravidity. The researchers found a surprising protective effect of placental malaria of primigravid mothers on their firstborns’ risk of parasitemia. Placental malaria of multigravid women, on the other hand, significantly increased risk of parasitemia during infancy. And even in the absence of



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**Section from a malaria-infected placenta (Photo: Michal Fried)**

placental malaria, firstborn children were less likely to have parasitemia than infants born to multigravid mothers. These results suggest that risk of parasitemia during infancy was modified by an interaction between placental malaria and gravidity.

Duffy and colleagues speculate that the stronger inflammatory response to placental malaria in first-time mothers could reduce congenital transmission or somehow strengthen the fetal immune system against malaria. They also suggest that the opposing effects of placental malaria in different gravid groups might explain why earlier studies found no significant risk between placental malaria and malaria susceptibility during the first two years of life. The results here are provocative but preliminary. Additional larger studies are necessary to conclusively demonstrate an interaction between placental malaria and gravidity in infant malaria susceptibility, and to examine potential modulation of congenital malaria transmission and infant immunity to the parasite by placental inflammation.

**Mutabingwa TK, Bolla MC, Li JL, Domingo GJ, Li X, et al. (2005) Maternal malaria and gravidity interact to modify infant susceptibility to malaria. DOI: 10.1371/journal.pmed.0020407**

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