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## **Measuring the impact of published scientific research in the developing world and among patient communities**

Richard Gedye  
Director of Outreach Programmes, STM

STM Publication Impact Seminar, Thursday 19 November 2015



# *patient* **INFORM**

ACCESS + INTERPRETATION = UNDERSTANDING + EMPOWERMENT



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The Research4Life initiative aims to reduce the knowledge gap between industrialized countries and developing countries by providing affordable access to critical scientific research from some 16,000 journals, 46,000 books, and 140 other information resources.

Over 8000 institutions in developing countries are currently registered for access to this content.

Research4Life partners include four United Nations Agencies, Yale and Cornell University Libraries, ProQuest, STM, and 208 publishers.



- 
- ❑ Institutions in 71 of the world's poorest countries receive free access to journal and book content via Research4Life
  - ❑ Institutions in a further 44 countries pay US \$1,500 per year for a subscription to the Research4Life content – an effective discount of over 99.9%

# Research4Life Programmes

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**Biomedicine**

[www.who.int/hinari](http://www.who.int/hinari)



**Agriculture**

[www.fao.org/agora](http://www.fao.org/agora)



**Environment**

[www.unep.org/oare](http://www.unep.org/oare)



**Innovation and  
Technology**

[www.wipo.int/ardi](http://www.wipo.int/ardi)



# Measuring the Impact of Research4Life

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- 14 years after the launch of Research4Life's first programme, HINARI, what do we know of its impact on its target communities?

# Measuring Impact – Stories & Statistics



## CONTROVERSIAL TOPICS, EDUCATION, RESEARCH

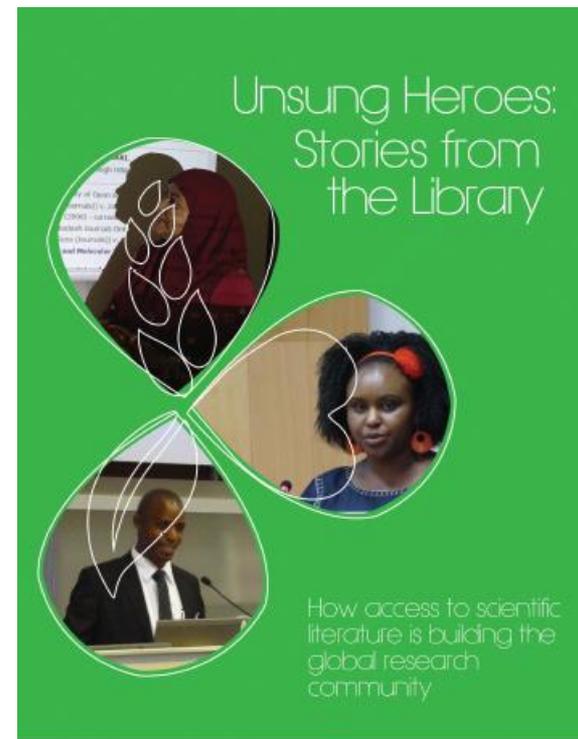
### Statistics and Storytelling — Why We Need Them Both in Science

POSTED BY PHIL DAVIS · NOV 15, 2011 · 8 COMMENTS

**FILED UNDER** EVIDENCE-BASED MEDICINE, JONATHAN A. EISEN, META-ANALYSIS, NARRATIVES, STATISTICS

Two thought-provoking articles published last week in JAMA make compelling and complementary arguments to the rhetorical power of both numbers and words in conveying the message of science.

# Measuring impact by “storytelling”



# Case Studies - Researchers & Practitioners

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## Making a difference

**Stories from the field:**  
how access to scientific literature  
is improving the livelihoods of  
communities around the world



# Research4Life has made an impact

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- ❑ allowed a doctor in Ethiopia to successfully treat a patient with a rare and serious condition, and helped his hospital to deliver more effective training to orthopaedic physicians
- ❑ helped a researcher from Burkina Faso to develop better and more informed scientific writing skills, produce focused research that he can discuss with top researchers worldwide, compete more effectively for research funding, and deliver better teaching programmes



# Research4Life has made an impact

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- enabled a Nepalese paediatrician to save children's lives through better treatment of diarrhoeal diseases, at the same time as developing his hospital's journal into a scientifically rigorous publication



- helped a physician to improve the lives of HIV-infected children in Zambia



# Research4Life has made an impact

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- allowed a Sudanese policy-maker to introduce evidence-based policy development designed to improve the Sudanese people's health in the long term
- enabled a midwife to improve maternity care in Zimbabwe and reduce maternal and neonatal mortality rates



# Research4Life has made an impact

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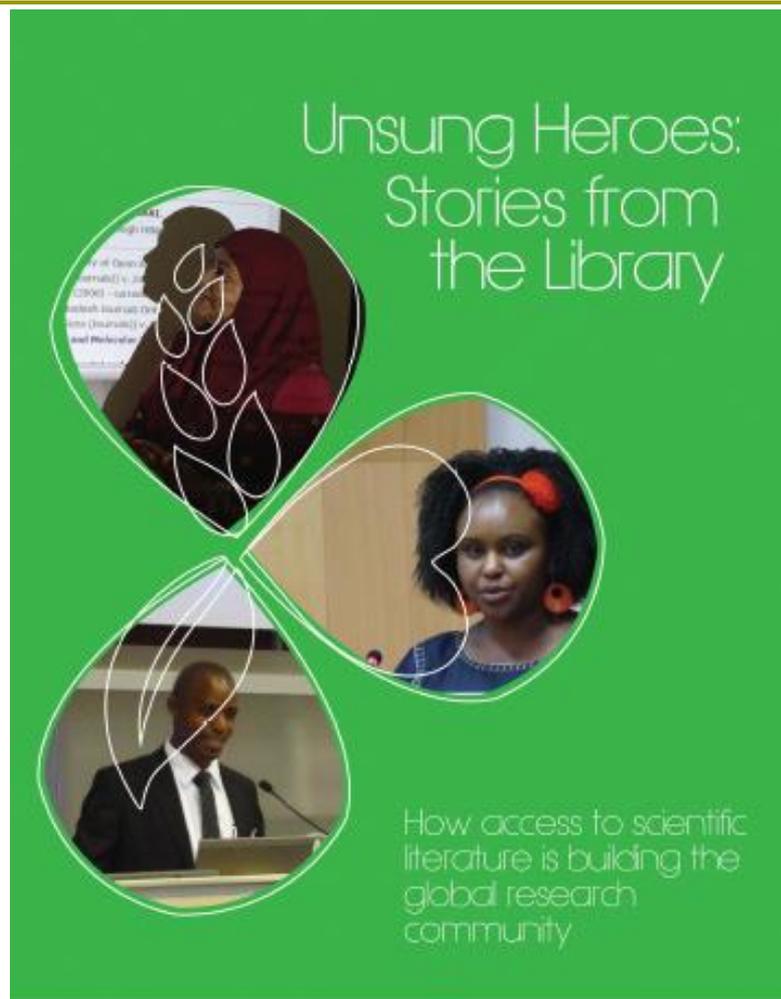
- ❑ Helped an Ethiopian physiotherapist find better ways to treat patients and teach his students
- ❑ See the video at <http://tinyurl.com/Research4Life>



Treating a patient with a spinal cord injury. Research4Life's HINARI programme has led to better results for patients and students, as well as Mr Bayisa himself.

# Case Studies - Librarians

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# Research4Life has made an impact

- A Ugandan agricultural scientist has drastically reduced the use of print resources, eliminating congestion in the libraries while boosting research and output.



- A Kenyan librarian has increased Research4Life usage across ten campuses, supporting research and demonstrating that digital is research's digital backbone.



- A Ugandan health professional has written her PhD on solving the problem of low Research4Life usage by developing a powerful training infrastructure for Ugandan universities.



# Research4Life has made an impact

- A Kenyan librarian has become an expert on information technology and electronic resources at her university, collaborating with doctors and nurses to find the research they need to effectively treat their patients. See the [video](#)
- A tech-savvy Honduran medical librarian has created a one-stop virtual medical library, resolving security issues which had previously prevented access.
- One of the early adopters in Nigeria has turned around medical and nursing curricula to include information literacy and Research4Life training.
- Another Ugandan librarian has introduced Research4Life at Makerere University, resulting in a substantial rise in research productivity.

# Measuring impact via statistics

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How to measure the impact of the Research4Life programmes statistically?

**Plan A: Bibliometric Analysis**

# Measuring impact bibliometrically

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## Proposal

- Identify institutions registered for HINARI at least four years ago with significant use of its content
- Examine their research output in the last 15 years
- Measure whether, since the introduction of access to HINARI content:-
  - there had been a significant increase in the production of research articles
  - there had been a significant increase in the number of cited references in these articles
  - article reference lists included more citations to HINARI journals
  - the median age of article references had decreased

# Measuring impact bibliometrically

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- Identify institutions registered for HINARI in the last 12 months.
  - Gather the same data on research article production over the last 15 years.
  
- Identify developing world institutions not registered for HINARI and with no formal institutional access to HINARI journals via any other means.
  - Gather the same data on research article production over the last 15 years.

# Measuring impact bibliometrically

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## **Problems with the bibliometric approach**

- ❑ After extensive research and consultation, we reluctantly concluded that a bibliometric analysis which could isolate the impact of HINARI from other confounding variables was not feasible

# Measuring impact bibliometrically

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- There is no data for developing country research-producing institutions that records
  - changes in the number of biomedical researchers
  - changes in the levels of funding for research
- Difficulty establishing whether institutions without access to HINARI journals via HINARI might have similar access via other means.
- Before HINARI access, there would be unlikely to be a sufficiently large body of published research from any given institution to allow a median article reference age trend to be measured.

# A statistical alternative to bibliometrics?

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“The plural of anecdote is data”

Professor Raymond Wolfinger, UC Berkeley

# Measuring impact via statistics

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How to measure the impact of the Research4Life programmes statistically?

**Plan B: A User Survey**

# Gathering more impact data

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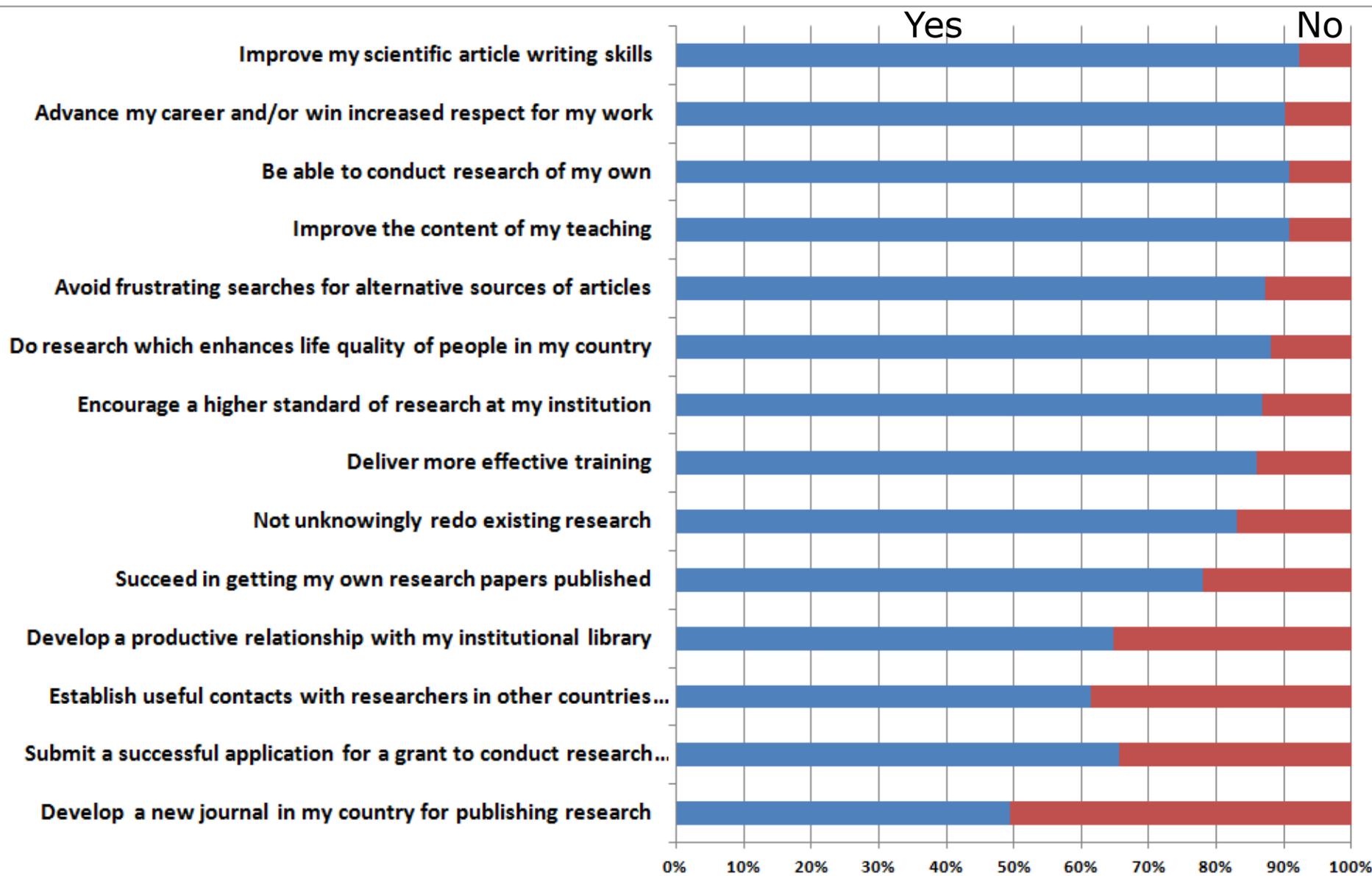
# Gathering more impact data

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- Last year we supplemented our case studies with a more extensive survey of HINARI users:-
  - 1034 Respondents
    - Researchers 46%
    - Physicians 32%
    - Students 15%
    - Administrators 4%
    - Librarians 3%

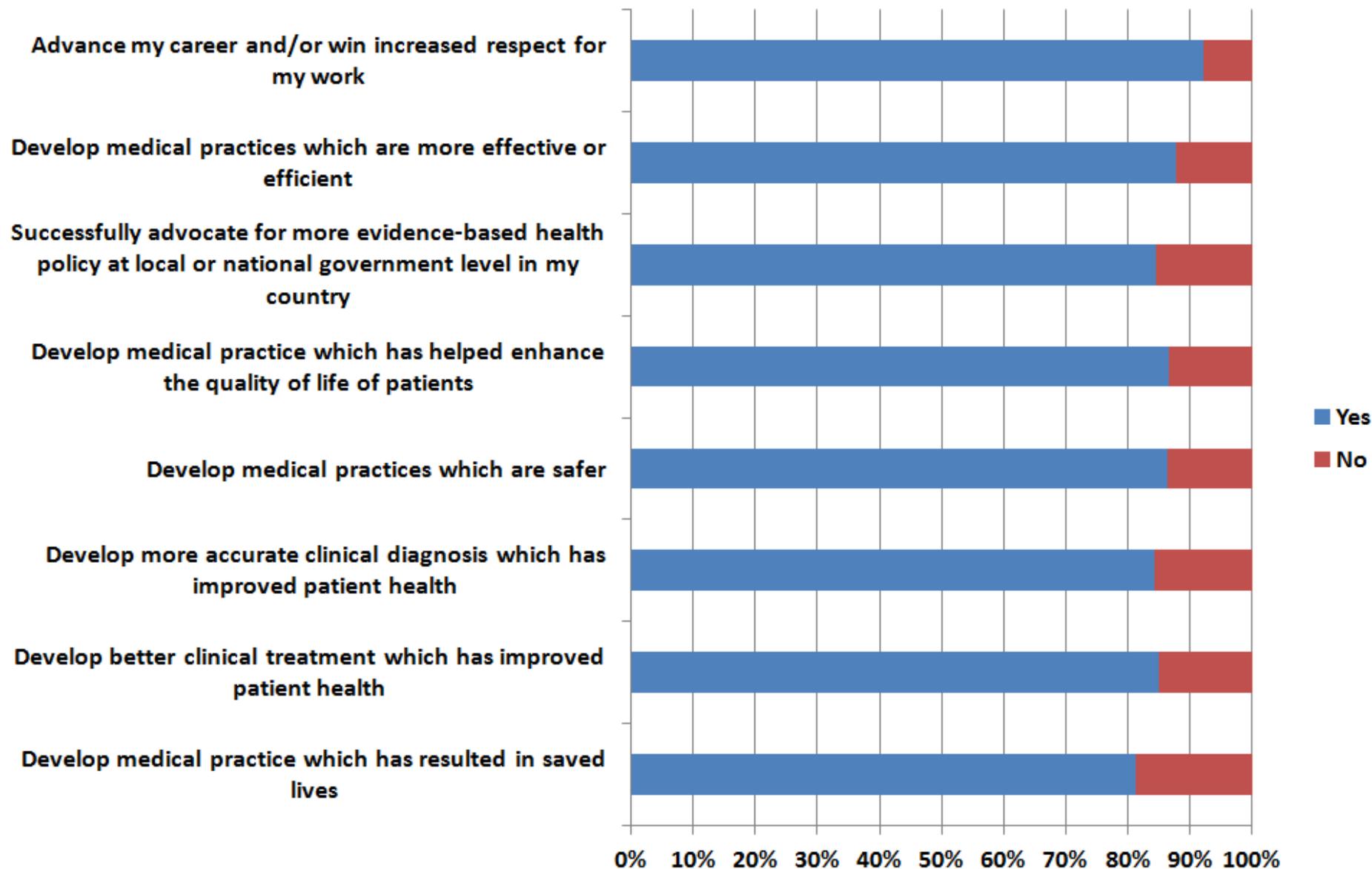
# Researchers: Having access to previous research via HINARI, has helped me:

n = 393-523



# Physicians: Having access to previous research via HINARI, has helped me:

n = 380-471



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- And lots of positive testimonials to the value of the HINARI programme
    - For us in developing countries, the value of HINARI cannot be overemphasized. It is impossible to conduct meaningful research without access to fulltext articles of previous research and only HINARI provides this for us in developing countries
    - HINARI and AGORA are the two sources which are complete and user-friendly to me and many colleagues of mine. In the absence if these sources, scientific research and manuscript preparation would be practically improbable to me and many others in Ethiopia.

# Access the Reports

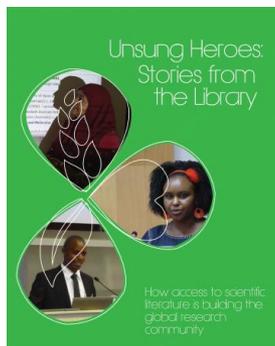
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[tinyurl.com/hinari-impact](http://tinyurl.com/hinari-impact)



[www.research4life.org/competitionbook](http://www.research4life.org/competitionbook)



[tinyurl.com/R4L-librarians](http://tinyurl.com/R4L-librarians)

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MASSACHUSETTS  
MEDICAL SOCIETY

Every physician matters, each patient counts.



OXFORD  
UNIVERSITY PRESS



WILEY



Wolters Kluwer  
Health

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# A carer's problem.....

*“I’m educated to degree level but my degree is in geography. Most research articles that relate to my son’s condition are couched in such detailed specialist scientific jargon and presuppose such an immense knowledge of biology, biochemistry, genetics, pharmacology etc that they might as well be written in Esperanto.”*

*“Even for any articles which are marginally more comprehensible, it is still just about impossible for me to know which, of the many hundreds that appear, represent significant advances in knowledge or significant steps in the quest for a treatment or cure.”*

# A recommended solution.....

- *Publishing a lay summary alongside every research article could be the answer to assisting in the wider understanding of health-related information.....*
- *Patients... want easy-to-understand, evidence-based information relating to biomedical and health research....*
- *Dr Liz Lyon, director of UKOLN, University of Bath explains, "The Patients Participate! Project has demonstrated the potential value of lay summaries to make research more accessible to a wider audience. ...."*
- *Medical research charities have an important role in providing patients and the public with information about the research they fund.*

# A recommended solution.....

- the Patients Participate! Report recommended publishing a lay summary alongside every research article and had two suggestions as to ways in which this might be achieved:-
  - Each researcher produces such a summary for each paper they publish, with training provided by their institutions and others to help them develop the communication skills necessary to share their findings with a lay audience and so bridge the understanding gap
  - Encourage, support and further leverage the role of medical research charities in providing patients and the public with information about the research they fund.

# *patient* **INFORM**

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patientINFORM:-

- Makes it easier for medical research charities, or voluntary health organisations (VHOs), to keep up to date with the latest research in their field by giving them unlimited access to around 1000 subscription based journals from participating publishers
- Provides a mechanism whereby VHO lay summaries of what they judge to be key articles can be linked to the full text of these articles without users encountering paywalls.
- This means that patients and carers can get an intelligible summary of the most significant and important latest research, but can also access and print out the research article on which the summary is based and share it with their physician, as part of their physician-patient dialogue on matters of disease progression and treatment.



## Research

A robust medical research effort is essential to find the causes of lupus, develop more effective treatments, and eventually cure the disease.

### Access: Lupus Research

[LFA Research Program](#) | Research Summaries

"Access: Lupus Research," produced in collaboration with patientINFORM, presents summaries of late-breaking research published in respected medical journals that report on lupus and related conditions.



In each category below, you can find summaries that explain the importance of recent research studies about lupus. All summaries provide access to the article abstract; select summaries provide access to the full journal article.

These summaries are intended to help you understand the latest lupus research, and help you and your family have more productive discussions with your doctors and make better-informed decisions about your health care. The information provided is not a substitute for advice from your own doctor or other health care providers. If you have questions about this material, please contact your doctor.

When you see the patientINFORM logo next to a summary, you'll know that the journal article it discusses comes from one of the medical journals participating in patientINFORM. Those summaries will have a link to the full journal article in PDF format.

Select a category to read the latest in lupus research summaries.

- ▶ [Animal Models](#)
- ▶ [Antiphospholipid Syndrome](#)
- ▶ [Apoptosis](#)
- ▶ [Blood Components](#)
- ▶ [Cancer](#)
- ▶ [Cardiovascular Disease](#)
- ▶ [Clinical Trials](#)



## Research

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## Research Summaries from 2012

### Autoantibody Profiling in People with Lupus

Measurement and monitoring of autoantibody levels in people with lupus can be useful in diagnosis and disease monitoring and also have the potential to illustrate the efficacy of drug therapies being taken for lupus over time. There are a number of autoantibodies that are important in lupus, including antibodies to double-stranded DNA (anti-ds-DNA), anti-Smith antibodies, and others, which may have to be tested or measured separately (which can be time-consuming and/or costly). The development of a single test that can simultaneously measure several different autoantibodies important in lupus could be important and useful. The results indicate that a single test can indeed accomplish this and suggest that most lupus patients can be categorized into at least one of two groups that have distinct kinds of autoantibody profiles with unique susceptibilities to specific kinds of lupus manifestations.

[Read more >>](#)



### Lupus Anticoagulant Affects Pregnancy Outcomes

Having antibodies typical of anti-phospholipid syndrome (APS) can increase the risk of pregnancy complications. However, whether or not specific women with APS, such as women who also have lupus, may be at even greater risk of pregnancy complications has not been fully established or agreed upon. Identification of specific women with APS or specific characteristics, such as the presence of specific APS antibodies, which can predict increased risk of adverse pregnancy outcomes, could be very useful. The results of this study highlight the important role of lupus anticoagulant, as well as that of a previous blood clot, in adverse pregnancy outcomes.

[Read more>>](#)



### Men Require More Lupus Genes to Develop Lupus

Lupus is thought to develop due to a combination of both genetic and environmental factors and is more common in women. Numerous studies have identified genes that increase the likelihood of developing lupus. The disparate incidence of lupus in women over men may be related to sex-specific genetic or hormonal factors. However, the degree to which these sex-specific factors favor the development of lupus in women over men has not been well established. The results of this study indicate that men require more lupus genes than women in order to develop lupus. The implications of these results are discussed in the context of possible sex- and hormone-related differences between men and women with lupus.

[Read more>>](#)



### Vitamin D Indicates Lupus Disease Activity But Not Organ Damage

Vitamin D promotes calcium absorption from the gut and also helps to maintain appropriate levels of calcium in the blood. It is essential for maintaining bone health, but also regulates immune functions. Vitamin D is normally produced in the body upon exposure to sunlight. However, since many people with lupus avoid sun exposure, they may be at risk for



## Men Require More Lupus Genes to Develop Lupus

### ▶ [Analysis of autosomal genes reveals gene-sex interactions and higher total genetic risk in men with systemic lupus erythematosus.](#)

Hughes T, Adler A, Merrill JT, Kelly JA, Kaufman KM, Williams A, Langefeld CD, Gilkeson GS, Sanchez E, Martin J, Boackle SA, Stevens AM, Alarcón GS, Niewold TB, Brown EE, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Criswell LA, Vilá LM, Jacob CO, Gaffney PM, Moser KL, Vyse TJ, Alarcón-Riquelme ME; BIOLUPUS Network, James JA, Tsao BP, Scofield RH, Harley JB, Richardson BC, and Sawalha AH. *Annals of the Rheumatic Diseases*. 2011 Nov 21. [epub ahead of print]

### What is the topic?

Lupus is thought to develop due to an interaction between genetic susceptibility and environmental triggers. Previous studies have identified a number of genes referred to as "lupus susceptibility genes," the presence of which are thought to increase the likelihood of developing lupus.

Importantly, lupus is about nine times more common in women than in men. This increased susceptibility may be made possible, at least in part, due to differences related to hormones and sex chromosomes. However, to what extent these sex differences contribute to the development of lupus is largely unknown.

### What did the researchers hope to learn?

The researchers hoped to learn about the degree to which sex-specific genetic differences contribute to the susceptibility to developing lupus. They also investigated possible sex-related differences in levels of anti-double-stranded DNA antibodies (anti-dsDNA) between men and women with lupus.

### Who was studied?

3936 people with lupus (3592 females and 344 males), as well as 3491 healthy people (2340 females and 1151 males), of European descent were studied.

### How was the study conducted?

- **What is the topic?**
- **What did the researchers hope to learn?**
- **Who was studied?**
- **How was the study conducted?**
- **What did the researchers find?**
- **What were the limitations of the study?**
- **What do the results means for you?**

is identical except for this one base, so male samples would generate a heterozygous genotype and female samples would generate a homozygous genotype. Samples with increased heterozygosity (>5SD around the mean) were then removed. Finally, genetic outliers were identified and excluded as determined by principal components analysis and admixture proportions calculated using ADMIXMAP, as previously described.<sup>16</sup> Samples included in the analysis consisted of 344 male patients

a total of 287 men and 2982 women with SLE.

## RESULTS

We first performed case-control association tests in men and women separately. The majority of associations previously reported in women-only or combined populations were recapitulated in our male patients (table 1). Moreover, three of these

**Table 1** Genetic associations in men and women with systemic lupus erythematosus compared with normal healthy male and female controls of European descent

SNP	Gene locus	Male				Female			
		Risk allele frequency				Risk allele frequency			
		Case	Control	OR (95% CI)	p Value	Case	Control	OR (95% CI)	p Value
rs2476601	<i>PTPN22</i>	0.102	0.081	1.28 (0.96 to 1.71)	0.089	0.110	0.0802	1.41(1.24 to 1.61)	$1.5 \times 10^{-7}$
rs1801274	<i>FCGR2A</i>	0.528	0.499	1.13 (0.94 to 1.34)	0.18	0.542	0.513	1.13 (1.05 to 1.21)	0.0017
rs2205960	<i>TNFSF4</i>	0.276	0.209	1.44 (1.19 to 1.75)	$2.3 \times 10^{-4}$	0.269	0.2167	1.33 (1.22 to 1.45)	$1.6 \times 10^{-10}$
rs7574865	<i>STAT4</i>	0.285	0.213	1.47 (1.21 to 1.79)	$1.2 \times 10^{-4}$	0.309	0.2302	1.49 (1.37 to 1.63)	$4.0 \times 10^{-20}$
rs231775	<i>CTLA4</i>	0.352	0.346	1.03 (0.86 to 1.23)	0.79	0.362	0.3475	1.07 (0.87 to 1.01)	0.11
rs11568821	<i>PDCD1</i>	0.878	0.875	1.03 (0.79 to 1.34)	0.83	0.889	0.8851	1.04 (0.93 to 1.18)	0.47
rs6445975	<i>PXK</i>	0.311	0.280	1.16 (0.96 to 1.40)	0.12	0.291	0.2564	1.19 (1.10 to 1.30)	$3.6 \times 10^{-5}$
rs10516487	<i>BANK1</i>	0.746	0.675	1.42 (1.17 to 1.72)	$4.3 \times 10^{-4}$	0.737	0.701	1.19 (1.10 to 1.30)	$2.8 \times 10^{-5}$
rs907715	<i>IL21</i>	0.680	0.655	1.12 (0.93 to 1.34)	0.23	0.687	0.656	1.15 (1.06 to 1.24)	$5.2 \times 10^{-4}$
rs3131379	<i>HLA Region 1</i>	0.222	0.099	2.61 (2.08 to 3.27)	$1.3 \times 10^{-17}$	0.172	0.0923	2.05 (1.82 to 2.30)	$1.7 \times 10^{-34}$
rs1270942	<i>HLA Region 2</i>	0.225	0.097	2.71 (2.16 to 3.40)	$5.9 \times 10^{-19}$	0.172	0.0921	2.05 (1.82 to 2.30)	$2.1 \times 10^{-34}$
rs729302	<i>IRF5</i>	0.737	0.684	1.23 (1.02 to 1.49)	0.032	0.745	0.675	1.41 (1.30 to 1.53)	$1.3 \times 10^{-16}$
rs2070197	<i>IRF5</i>	0.204	0.106	2.15 (1.71 to 2.69)	$2.6 \times 10^{-11}$	0.172	0.1028	1.82 (1.62 to 2.03)	$9.3 \times 10^{-26}$
rs10954213	<i>IRF5</i>	0.699	0.639	1.31 (1.09 to 1.58)	0.0038	0.678	0.618	1.30 (1.21 to 1.41)	$1.9 \times 10^{-11}$
rs13277113	<i>C8orf13-BLK</i>	0.321	0.229	1.60 (1.32 to 1.93)	$1.3 \times 10^{-6}$	0.288	0.2421	1.27 (1.16 to 1.38)	$6.5 \times 10^{-8}$
rs1800450	<i>MBL</i>	0.143	0.140	1.03 (0.80 to 1.31)	0.83	0.146	0.1392	1.05 (0.85 to 1.06)	0.34
rs4963128	<i>KIAA1542</i>	0.664	0.673	0.96 (0.80 to 1.15)	0.68	0.712	0.664	1.25 (1.15 to 1.35)	$4.7 \times 10^{-8}$
rs1143679	<i>ITGAM</i>	0.201	0.138	1.57 (1.26 to 1.96)	$5.4 \times 10^{-5}$	0.193	0.1202	1.75 (1.58 to 1.95)	$1.3 \times 10^{-25}$

SNP, single nucleotide polymorphism.

associations attained genome-wide significance ( $p < 5.0 \times 10^{-8}$ ) in men. We then compared risk allele frequencies between men and women with SLE (table 2).

Interestingly, the frequency of the risk alleles in the HLA locus was significantly higher in men than in women with SLE (rs3131379:  $OR_{\text{male-female}}$  1.37 (95% CI 1.14 to 1.66),  $p=0.0010$ ; rs1270942:  $OR_{\text{male-female}}$  1.40 (95% CI 1.16 to 1.69),  $p=0.00046$ ). This was also the case for an SNP in *IRF5* (rs2070197:  $OR_{\text{male-female}}$  1.23 (95% CI 1.01 to 1.49),  $p=0.039$ ). It is important to note that there was no difference in the risk allele frequencies in the control group between men and women ( $p=0.39$ , 0.52 and 0.64, for rs3131379, rs1270942 and rs2070197, respectively). Therefore, it was not surprising to see a trend for a higher association OR in men than in women in sex-specific case-control analysis in these loci (figure 1). This trend was further examined by calculating the heterogeneity  $I^2$  index (range 0–100) and Q statistic p values to assess heterogeneity between male and female case-control ORs (rs3131379:  $OR_{\text{male}}$  2.61 (95% CI 2.08 to 3.27),  $OR_{\text{female}}$  2.05 (95% CI 1.82 to 2.30),  $I^2$  index=71.69 and Q statistic  $p=0.060$ ; rs1270942:  $OR_{\text{male}}$  2.71 (95% CI 2.16 to 3.40),  $OR_{\text{female}}$  2.05 (95% CI 1.82 to 2.30),  $I^2$  index=78.68, Q statistic  $p=0.030$ ; rs2070197:  $OR_{\text{male}}$  2.15 (95% CI 1.71 to 2.69),  $OR_{\text{female}}$  1.82 (95% CI 1.62 to 2.03),  $I^2$  index=39.73, Q statistic  $p=0.20$ ). A post hoc analysis showed that our study had 100%

power to detect genetic associations in the HLA region and *IRF5* in men ( $\alpha=0.05$ ), suggesting that a smaller sample size of men than women in our study did not result in inflation of the ORs in our male set.<sup>20 21</sup>

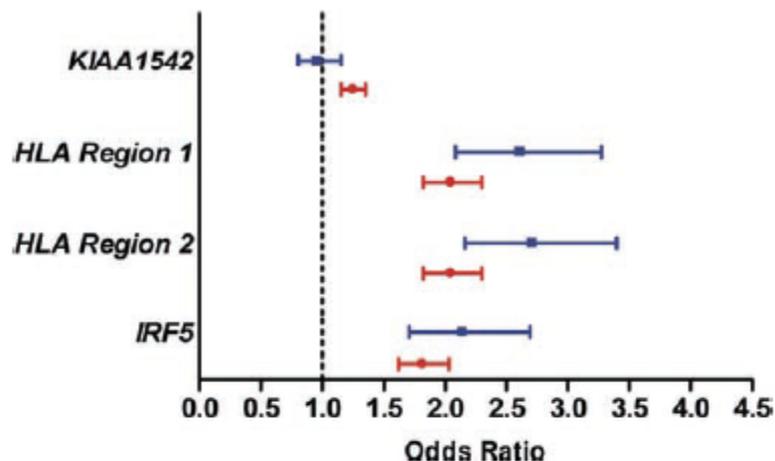
Significant allelic differences between men and women with SLE were also observed for rs4963128, a polymorphism located in *KIAA1542* ( $OR_{\text{male-female}}$  1.25 (95% CI 1.06 to 1.48),  $p=0.0095$ ) (table 2). rs4963128 was associated with SLE in women but not in men in our study ( $OR_{\text{male}}$  0.96 (95% CI 0.80 to 1.15),  $p=0.68$ ;  $OR_{\text{female}}$  1.25 (95% CI 1.15 to 1.35),  $p=4.7 \times 10^{-8}$ ;  $I^2$  index=84.79, Q statistic  $p=0.010$ ).

We next used a case-only pairwise epistasis analysis implemented in PLINK and confirmed the sex-gene interactions found (table 3). We further validated our results using a non-parametric methodology for non-linear epistasis by applying the MDR test (table 3).

Genetic differences associated with anti-dsDNA antibody positivity among patients with SLE were recently reported by Chung *et al.*<sup>22</sup> We investigated sex differences in the prevalence of anti-dsDNA antibodies among our test population to account for possible confounding. No significant difference in the presence of anti-dsDNA antibodies between men and women with SLE was observed ( $p=0.15$ ). As men with SLE have previously been reported to experience more severe disease than women, it is important to examine if the difference in the frequencies of the HLA region risk alleles and the risk alleles in *IRF5* and *KIAA1542* that we observed between men and women is not influenced by differences in disease severity. We determined the frequencies of severe SLE manifestations in men and women included in the study (renal involvement, neurological involvement, serositis and thrombocytopenia) and found no differences in the frequencies of neurological involvement or serositis between men and women. However, consistent with previous reports, men with SLE in our study were almost twice as likely to have renal involvement as women ( $OR$  1.70 (95% CI 1.34 to 2.17),  $p=1.2 \times 10^{-5}$ ). Likewise, men with SLE were more likely to have thrombocytopenia ( $OR$  2.26 (95% CI 1.62 to 3.15),

**Table 2** Sex-gene disparities between men and women with systemic lupus erythematosus

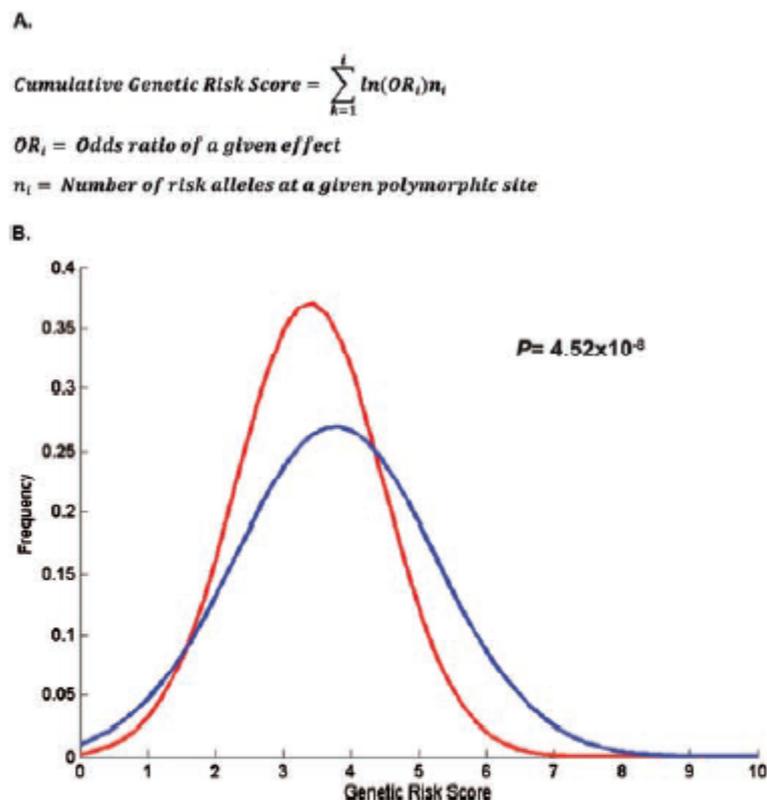
SNP	Gene	Risk allele frequency					p Value
		Male	Female	OR	95% CI LL	95% CI UL	
rs2476601	<i>PTPN22</i>	0.102	0.110	1.08	0.84	1.40	0.55
rs1801274	<i>FCGR2A</i>	0.528	0.542	1.06	0.90	1.24	0.48
rs2205960	<i>TNFSF4</i>	0.276	0.269	1.04	0.87	1.24	0.67
rs7574865	<i>STAT4</i>	0.285	0.309	1.12	0.94	1.34	0.21
rs231775	<i>CTLA4</i>	0.352	0.362	1.05	0.89	1.23	0.60
rs11568821	<i>PDCD1</i>	0.878	0.889	1.11	0.87	1.42	0.38
rs6445975	<i>PYK</i>	0.311	0.291	1.10	0.93	1.30	0.27



**Figure 1** Sex-specific differences in genetic associations in systemic lupus erythematosus (men in blue and women in red).

and  $p=1.00$ , respectively). These data indicate that the difference in allele frequency between men and women with SLE in the HLA region, *IRF5* and *KIAA1542* is not explained by a higher frequency of renal involvement or thrombocytopenia in men than in women.

We further investigated sex-specific differences in overall SLE genetic risk between men and women by calculating a cumulative genetic risk score for SLE in each individual included in the study. Scores were calculated based on the ORs obtained in the sex-specific case-control association analyses using the equation shown in figure 2A. Using a Student t test we observe that, on average, male patients have a significantly higher genetic risk than female patients ( $p=4.52 \times 10^{-8}$ ; figure 2B). Interestingly, but not unexpectedly, the gap between men and women widens upon removal of rs4963128 (*KIAA1542*), the effect specific to women, while the disparity narrows as one HLA SNP is removed and the difference disappears entirely when both HLA SNPs are taken away ( $p=0.30$ ).



**Figure 2** (A) The equation by which cumulative genetic risk scores were calculated. Scores were obtained for each patient by multiplying the natural logarithm of the OR for each of the associated loci by the number of risk alleles present at each locus. Cumulative risk was then calculated in each patient by summing the risk scores for 15 out of 18 risk loci included in this study. Three loci were not included when calculating the cumulative genetic risk scores because they were not associated with systemic lupus erythematosus in our study (*CTLA4*, *PDCD1* and *MBL*). (B) Distribution curves for cumulative genetic risk scores for systemic lupus erythematosus in men (blue) and women (red) showing a higher genetic risk in men than in women ( $p=4.5 \times 10^{-8}$ ). Sex-specific ORs (table 1) were used to calculate the cumulative genetic risk score in male and female patients.

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