# Cardiovascular disease research output in WHO priority areas between 2002 and 2011

Laura Myers, Shanthi Mendis

http://www.elsevier.com/locate/jegh

# Cardiovascular disease research output in WHO priority areas between 2002 and 2011

## Laura Myers [*], Shanthi Mendis [1]

*World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland*

**Abstract** Approximately 17.3 million people died from cardiovascular disease (CVD) in 2008, and approximately 80% came from low- and middle-income countries. However, previous studies document poor research productivity related to CVD prevention and treatment in these countries between 1991 and 1996. The World Health Organization (WHO) developed a prioritized research agenda emphasizing research on policy development, translation of knowledge and implementation. This study assessed whether research output in priority areas increased between 2002 and 2011. It was reported that only 3–4% of papers from each year related to a priority area, and most were conducted by corresponding authors from high-income countries. Low-income countries were highly underrepresented both in terms of productivity and as the study population. However, there was a significant rise in the productivity of middle-income countries and their representation as the study population. While 30% of priority-related papers addressed a cost-effective strategy, this represents 1% of papers overall. More cost-effectiveness research is encouraged to decrease the millions of deaths per year attributed to CVD in the developing world.

## 1. Introduction

Cardiovascular diseases (CVDs) refer to coronary artery disease, cerebrovascular disease, peripheral vascular disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary vascular disease. Collectively, these seven diseases are the number one cause of death globally [1]. A report from the World Health Organization (WHO) estimates that 17.3 million people died from CVDs in 2008, and 80% of these cases occurred in low- and middle-income countries [2]. It is thought that people in resource-poor countries have less access to preventive services, less access to medications and procedures, and more exposure to risk factors such as tobacco exposure and

[*] Corresponding author. Permanent Address: Massachusetts General Hospital, BMG, Wang Ambulatory Care Center, 5th floor, 15 Parkman St., Boston, MA 02114, USA. Tel.: +617 724 6620.
  *E-mail addresses:* lcmyers@partners.org (L. Myers), mendiss@who.int (S. Mendis).
  [1] Tel.: +41 22 791 3612.

fat-laden foods. Unfortunately, this means that countries with the fewest resources to conduct research on risk factors and cost-effective interventions carry the burden of disease.

While some treatments for these diseases are expensive (CABG, stenting, valve replacements, and pacemakers), many are affordable to all countries (aspirin, insulin, generic anti-hypertensives, generic statins, and nicotine replacement). A systematic review by Shroufi et al. [3] published in 2013 examined the number and type of cost-effective interventions for CVDs that were done in low- and middle-income countries in 2010. These included both behavioral and pharmacologic interventions where cost per disability-adjusted life-year was less than 1-3 times the gross national income per capita. Of the 9729 papers obtained in the original search, the list was narrowed to 16 papers that addressed the following four broad categories: medications to lower blood pressure and cholesterol [4—14]; tobacco control (through nicotine patch, bupropion, and price control of cigarettes) [15,16]; intervention through mass media (diet modification, reduced salt intake, and smoking cessation) [17,18]; and intervention through legislation (mandatory lowering of salt added to mass-produced food) [19]. If a country's limited resources were allocated to these cost-effective, data-proven strategies, one could imagine a significant reduction in the CVD morbidity and mortality in low- and middle-income countries.

However, these cost-effective strategies need to be adapted for and validated in specific populations prior to being implemented broadly. A paper by Mendis et al. [20] documented low CVD research output from low- and middle-income countries between 1991 and 1996. They report that 82 developing countries, which represent 11% of the global population, did not publish a single paper in their random sample [20]. This data indicates that the amount of meaningful research that contains outcomes-based data on cost-effective strategies in low- and middle-income countries must be increased.

This study sought to assess the progress of CVD research output in the last decade between 2002 and 2011. A sample of a large number of papers from each year was chosen and it was determined if they addressed one of the four broad categories published by the WHO as priority research areas (Table 1) [21]. The country of origin of the corresponding author and study population, the type of study, the presence of cost-effective strategies and the language of publication (Table 2) were analyzed to get a better sense of the features of the priority-related papers published during this timeframe.

## 2. Materials and methods

Medline was searched using the MeSH term ''Cardiovascular Diseases'' and a year filter of 2002 and 2011; 3000 publications from each year in any language and from any country were examined by a physician, who read the abstracts and decided if the topic related at all to a WHO priority area. The original article was obtained if categorization was unclear. Each paper was assigned to one priority area that fit it best. The physician recorded the country of origin of the corresponding author and the study population. The World Bank list of economies from November 2011 was used to classify these countries by income level.

Fisher's Exact test was used to assess statistical significance in research output over time (Table 1). It was also used to assess statistical significance in research output over time with the corresponding authors from high vs. a combined group of low- and middle-income countries, and research output over time studying populations from high vs. a combined group of low- and middle-income countries. Papers were classified as being a north to north collaboration (corresponding author and study population from a high-income country), north to south collaboration (corresponding author from a high-income country and study population from a middle- or low-income country, respectively), or south to south collaboration (corresponding author and study population from low- or middle-income country). North to south and south to south collaborations were compared with north to north collaborations using Fisher's Exact test (Table 2).

Similarly, Fisher's Exact test was used to assess statistical significance in the type of publication over time (Table 2). For example, the number of clinical papers (that were not RCTs or survey-based) was compared with the combined group of all other types of publications published over time. Finally, Fisher's Exact test was used to assess statistical significance for the number of publications with cost-effective strategies over time and number published in a language other than English over time (Table 2).

## 3. Results and discussion

There were 47,897 cardiovascular disease publications indexed in 2002 and 54,488 in 2011, which increased overall from 35,000 in 1991 to 39,000 in

**Table 1** Distribution of Papers in 20 WHO Priority Areas for NCD Research.

|  |  | 2002 (*N*; %) | 2011 (*N*; %) | *p*-Value |
|---|---|---|---|---|
| A | Research to placing NCDs in the global development agenda and for monitoring NCDs and NCD risk factors | 40; 44% | 51; 47% | *p* = 0.7 |
| B | Intersectoral and multidisciplinary research to understand and influence the macroeconomic and social determinants of NCDs and exposure to NCD risk factors | 24; 26% | 25; 23% | *p* = 0.7 |
| C | Translation research and health system research for global application of proven cost-effective strategies | 27; 29% | 32; 30% | *p* = 1.0 |
| D | Research to enable expensive but effective interventions to become accessible and used appropriately in resource constrained settings | 1; 1% | 0 | N/A |

Data are shown from 2002 and 2011. Each column contains the number (*N*) and percentage (%) of papers that related to priority areas, A—D, on the left.

**Table 2** Characteristics of Priority-area Papers.

|  | 2002 (*N*; %) | 2011 (*N*; %) |  |
|---|---|---|---|
| *Income Level of Country of Origin of Study Population* |  |  |  |
| High income | 78; 85% | 78; 72% | *p* = 0.03 |
| Middle income | 14; 15% | 27; 25% |  |
| Low income | 0 | 3; 3% |  |
| *Income Level of Corresponding Authors' Country of Origin* |  |  |  |
| High income | 83; 90% | 83; 77% | *p* = 0.01 |
| Middle income | 9; 10% | 23; 21% |  |
| Low income | 0 | 2; 2% |  |
| *Collaborations* |  |  |  |
| North author to north study population | 78; 85% | 78; 72% | *p* = 0.05 |
| North author to south study population | 5; 5% | 5; 5% |  |
| South author to south study population | 9; 10% | 25; 23% |  |
| *Type of Publication* |  |  |  |
| Clinical (not randomized or survey-based) | 48; 52% | 75; 69% | *p* = 0.01 |
| Prevalence or Incidence Surveys | 16; 17% | 15; 14% |  |
| Review (including systematic) | 15; 16% | 5; 5% | *p* = 0.01 |
| Randomized Controlled Trial (RCT) | 3; 3% | 4; 4% |  |
| Comment | 3; 3% | 3; 3% |  |
| Historical, News or Editorial | 3; 3% | 3; 3% |  |
| Meta-analysis | 1; 1% | 1; 1% |  |
| Case Report | 2; 2% | 0 |  |
| Meeting Abstract or Report | 1; 1% | 0 |  |
| Practice Guidelines | 0 | 0 |  |
| Contains a Cost-effective Strategy | 3; 3% | 5; 5% | *p* = 0.73 |
| Published in Language other than English | 8; 9% | 13; 12% | *p* = 0.49 |

Data are shown from 2002 and 2011. The number (*N*) and percentage (%) of papers are listed. The *p*-values for study population, corresponding author and collaborations were calculated by combining low- and middle income groups and north-south and south-south groups. The *p*-values for the type of publication were calculated by comparing to a combined group of all other publication types listed. The *p*-values for cost-effective strategy and language other than English were calculated by comparing to the number not including a cost-effective strategy and not published in English, respectively.

1996 [20]. Of 3,000 randomly selected research papers in each year, a small percentage (only 3% from 2002 and 4% from 2011) related to a WHO priority area.

Of the 3—4% of papers that related to a WHO priority area, a large percentage addressed priority A, which identified NCD risk factors, NCD monitoring and placing of NCD prevention on the global agenda

(44% from 2002 and 47% from 2011, Table 1). These papers were mainly epidemiologic and survey-based data, and many simply stated the problem of a growing worldwide prevalence of CVD without actually testing interventions to curb the growing incidence. Group B papers identified macroeconomic and social determinants of NCD health, including exposures to risk factors and the effect of a tax on tobacco. Group C papers were translational and health systems research focused on implementing cost-effective interventions in resource-poor settings and addressing barriers to access. Only 1 paper was classified as related to area D, which addressed implementing expensive but effective interventions in resource-poor settings, so statistical significance could not be interpreted with such a small N (Table 1). The number of priority-related publications in areas A, B or C did not rise significantly over time ($p = 0.7$, $p = 0.7$, $p = 1$, respectively, Table 1). These data indicate that few papers overall are addressing the effects of implementing new policies, cost-effective interventions and alternative healthcare delivery models, and that the number has not risen between 2002 and 2011.

Looking more closely at the priority-related papers, there was a statistically significant rise in papers studying populations in the combined group of low- and middle-income countries ($p = 0.03$, Table 2), but the contribution of papers studying low-income countries was persistently low (0% and 3%, Table 2). In terms of corresponding authors' country of origin, most papers were published with a corresponding author from a high-income country (90% in 2002 and 77% in 2011, Table 2). Two countries published a large portion of these papers. The USA produced 21% of all priority-related papers in 2002 and 19% in 2011, and the UK produced 21% in 2002 and 12% in 2011 (Data not shown). Interestingly, the combined output from low- and middle-income countries doubled over time, which was a statistically significant change ($p = 0.01$, Table 2), but the absolute contribution from low-income countries was still minimal in both years (0% and 2%, Table 2).

The above relationships were further analyzed by comparing the type of collaboration over time. There was a barely statistically significant rise in the combined number of north to south and south to south collaborations over time compared with north to north collaborations ($p = 0.05$, Table 2). This rise is an important first step in promoting research in the developing world. Regardless of whether corresponding authors hail from high-income countries or native low- and middle-income

countries, the goal is to increase ethical CVD research in study populations from the south who experience the greatest burden of CVD.

The type of publication was also assessed over time. There was a statistically significant rise in clinical papers that were not randomized controlled trials (RCT) or survey-based when compared with a combined group of all other types of priority-related papers (52—69%, $p = 0.01$, Table 2). Conversely, there was a statistically significant decrease in reviews that included systematic reviews (16—5%, $p = 0.01$, Table 2). The overall contribution of RCTs was low in each year (3% and 4% of papers, respectively, Table 2). Of the 7 RCTs in both years, six were north to north collaborations, while the remaining one was a south to south collaboration and contained a cost-effective strategy for BP control in low-income countries (data not shown). More RCTs, specifically those containing a cost-effective intervention, are needed to prove efficacy of a cost-effective intervention in a certain population.

There was no significant change over time in the number of papers directly assessing cost-effective strategies or the number of papers published in a language other than English ($p = 0.73$ and $p = 0.49$, respectively, Table 2). However, of the papers published in a language other than English, a disproportionately high percentage had a corresponding author from middle-income countries (38% from 2002 and 46% from 2011, data not shown), which raises the concern that papers published in languages other than English are less accessible to be read and appreciated by the greater scientific community.

The limitations of this study include sampling error and the use of corresponding author to identify the country of origin of researchers.

## 4. Conclusions

It is encouraging that research output has increased from middle-income countries between 2002 and 2011 and that populations from middle-income countries are increasingly the subject of research. However, low-income countries remain disproportionately underrepresented for both the corresponding author and the study population. There is hope to see more low-income countries for the study population going forward. As long as research is performed ethically with the local disease burden, culture and economy as the focus, this research encourages both north to south collaborations and south to south collaborations. It is also hoped to see more RCTs so that the effect

of the interventions can be trusted and not attributed to bias.

Furthermore, there is an ongoing need for research on cost-effective CVD prevention and treatment strategies. While 30% of priority-related papers addressed cost-effective interventions, this means that 1% of papers overall look at cost-effective strategies, which is simply insufficient when paired against the millions of deaths that are attributed to CVDs per year.

Given the current availability of cost effective and affordable interventions for CVD, researchers must find ways to implement them in low- and middle-income countries and measure the effect of the interventions. New strategies must also be developed that are country- and population-specific to strengthen CVD prevention by improving access to healthcare either through changes in local policy or healthcare financing/delivery models. As a global community, the enormous potential to save lives and come together to make a difference must be recognized.

## 5. Conflicts of interest

The authors deny any financial, academic or personal conflicts of interest.

## 6. Disclosure

Dr S Mendis is staff member of the World Health Organization. The views expressed in the document by the author are solely the responsibility of the author. This document is not a formal publication of the World Health Organization (WHO).

### Acknowledgements

## References

[1] Global status report on noncommunicable diseases 2010. Geneva, World Health, Organization, 2011.

[2] Global atlas on cardiovascular disease prevention and control. Geneva, World Health, Organization, 2011.

[3] Shroufi A, Chowdury R, Achala R, Stevens S, Blanco P, Han T, et al. Cost effective interventions for the prevention of cardiovascular disease in low and middle income countries: a systematic review. BMC Public Health 2013;13:285.

[4] Huang G, Gu D, Wu X, Duan X, et al. Cost-effectiveness analysis of Beijing Fangshan cardiovascular prevention program in 1992—1997. Zhonghua Yu Fang Yi Xue Za Zhi 2000;34(2):78—80.

[5] Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet 2006;368(9536):679—86.

[6] Caro J, Klittich W, McGuire A, Ford I, et al. International economic analysis of primary prevention of cardiovascular disease with Pravastatin in WOSCOPS. West of Scotland Coronary Prevention Study. Eur Heart J 1999;20(4):263—8.

[7] Rubinstein A, García Martí S, Souto A, Daniel F, et al. Generalized cost-effectiveness analysis of a package of interventions to reduce cardiovascular disease in Buenos Aires, Argentina. Cost Effectiveness and Resource Allocation: C/E 2009;7:7—10.

[8] Ha DA, Chisholm D. Cost-effectiveness analysis of interventions to prevent cardiovascular disease in Vietnam. Health Policy Plan 2010;26:210—22.

[9] Gaziano TA, Steyn K, Cohen DJ, Weinstein M, et al. Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood pressure level. Circulation 2005;112(23):3569—76.

[10] Scuffham PA, Kósa J. The cost-effectiveness of fluvastatin in Hungary following successful percutaneous coronary intervention. Cardiovasc Drugs Ther 2006;20(4):309—17.

[11] Murray CJ, Lauer JA, Hutubessy RC, Niessen L, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet 2003;361(9359):717—25.

[12] Robberstad B, Hemed Y, Norheim OF. Cost-effectiveness of medical interventions to prevent cardiovascular disease in a sub-Saharan African country-the case of Tanzania. Cost Effectiveness and Resource Allocation: C/E 2007;5:3.

[13] Redekop WK, Orlewska E, Maciejewski P, Rutten FF, Niessen LW. Costs and effects of secondary prevention with perindopril in stable coronary heart disease in Poland: an analysis of the EUROPA study including 1251 Polish patients. Pharmacoeconomics 2008;26(10):861—77.

[14] Araujo D, Bahia L, Souza C. Cost-effectiveness and budget impact analysis of rosuvastatin and atorvastatin for LDL-cholesterol and cardiovascular events lowering within the SUS scenario. Int J Atheroscler 2007;2(3):189—94.

[15] Gilbert AR, Pinget C, Bovet P, Cornuz J, et al. The cost effectiveness of pharmacological smoking cessation herapies in developing countries: a case study in the Seychelles. Tob Control 2004;13(2):190—5.

[16] Thavorn K, Chaiyakunapruk N. A cost-effectiveness analysis of a community pharmacist-based smoking cessation programme in Thailand. Tob Control 2008;17(3):177—82.

[17] Akkazieva B, Chisholm D, Akunov N, Jacab M. The health effects and costs of the interventions to control cardiovascular disease in Kyrgyzstan 2009. Published by WHO. Available from: http://www.un.org.kg/en/publications/article/publications/by-agency/61-world-health-organization-(who)/4788-the-health-effects-and-costs-of-the-interventions-to-control-cardiovascular-disease-in-kyrgyzstan.

[18] Jamison DT. Disease control priorities in developing countries. Washington: IBRD/The World Bank and Oxford University Press; 2006. Chapter 44.

[19] Chisholm D, Doran C, Shibuya K, Rehm J. Comparative cost-effectiveness of policy instruments for reducing the global burden of alcohol, tobacco and illicit drug use. Drug Alcohol Rev 2006;25(6):553—65.

[20] Mendis S, Yach D, Bengoa R, Narvaez D, Zhang X. Research gap in cardiovascular disease in developing countries. Lancet 2003;361:2246—7.

[21] A Prioritized Research Agenda for Prevention and Control of Noncommunicable Diseases. World Health Organization, Geneva. 2011, 44—6.

Available online at www.sciencedirect.com

**ScienceDirect**