

IMPROVING OUTCOMES

FOR **NONCOMMUNICABLE DISEASES** IN
LOW- AND MIDDLE-INCOME COUNTRIES

KENNETH A. LABRESH, MD, EDITOR



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RTI Press

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Contents

Foreword	v
Preface	ix
Introduction	xi
1. Barriers to Screening, Diagnosis, and Treatment of Oral Cancers in India	1
Sujha Subramanian, Sonja Hoover, and Patrick Edwards	
2. Addressing the Challenge of Cervical Cancer Screening: Foundational Work in Karnataka, India	11
Suneeta Krishnan, Mahima Ashok, Laura Nyblade, Deborah Porterfield, and Melissa Stockton	
3. Microsimulation Models to Assess Impact of Health Programs to Address Obesity and Low Birth Weight in Indonesia	35
Philip C. Cooley, Susan M. Rogers, Christine Poulos, Matthew D. Scruggs, James I. Rineer, William D. Wheaton, Benjamin T. Allaire, and Diane Wagener	
4. Supporting Diabetes Medication Understanding and Adherence Through a Health Literacy Intervention, Meducation, in Kerala, India	61
Jonathan S. Wald, N.S. Vishwanath, Madhu Shrestha, Christine Poulos, Leena Simon, and Gadhadharan Vijayakumar	
5. Implementing “Get With The Guidelines” Stroke Program to Improve Health Outcomes of Acute Ischemic Stroke Patients in Shanghai, China	79
Zhi-Jie Zheng and Kenneth A. LaBresh	
6. Encouraging Primary Care Physicians to Talk With Their Patients About Stroke Risk Factors: A Brief Intervention in Indonesia	93
Pamela A. Williams and Kenneth A. LaBresh	
7. Deciphering Chronic Kidney Disease of Unknown Etiology in Sri Lanka	105
Jennifer Hoponick Redmon, Myles F. Elledge, Kamani P. Wanigasuriya, Rajitha Wickremasinghe, and Keith E. Levine	
8. RTI International Grand Challenge: Improving Outcomes of Noncommunicable Diseases—What Did We Learn?	127
Kenneth A. LaBresh, Michael T. Halpern, and Kathleen N. Lohr	
Contributors	135

Foreword

The banner of “noncommunicable diseases” (NCDs) was unfurled for the 2011 United Nations General Assembly meeting in New York City. It revealed an endemic global problem of severe chronic illnesses affecting the health and well-being of people around the world and undermining economic development. From the start, this grouping of diseases was intended to be inclusive, providing a convenient framing for four diseases with four common risk factors (the 4-by-4 rubric): cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases, with tobacco use, excess alcohol use, unhealthy diet, and physical inactivity as their main causes. The messaging worked. Global professional societies representing these chronic conditions joined together and coined the term NCD with the hope that collective action would increase public awareness, mobilize attention and financing, and stem the dramatic changes in disease burden that were affecting virtually the entire developing world. There would be power in numbers, they believed.

Proponents encountered struggles along the way as the 4-by-4 framework did not do justice to the range of biological, epidemiological, physical, and emotional experiences seeking shelter under the NCD banner. In recent years, the banner has been stretched in new directions as other debilitating diseases—such as mental and neurological conditions, rheumatic heart disease, and more exotic conditions strongly related to poverty—adopted the moniker and made common cause with the NCD movement.

I began working on global NCDs well more than a decade ago, coming to the topic from a background in agricultural development and undernutrition. Inspired by Derek Yach, who had recently created history at the World Health Organization by spearheading the Framework Convention on Tobacco Control, I became interested in the “overnutrition” end of the spectrum. As a program officer at the US National Institutes of Health, I was in a position to encourage research and research training on obesity and related diseases in poor countries. Initially that meant talking with a few colleagues about such questions as whether obesity is a risk factor or a disease (a seemingly innocuous question of great importance for NIH funding).

The world has changed in the past decade, and the global health community is changing as well. People who care about nutrition now care

about malnutrition in all its forms; people who pay for antiretrovirals for people living with HIV/AIDS now want to prevent those same people from dying of heart disease; people who care about economic development and jobs now focus on the productivity losses of premature illness and death; and people who care about poverty know that NCDs are both cause and consequence of poverty and must be slowed for UN Sustainable Development Goal 1, to end poverty in all its forms everywhere. Rolling out the NCD banner in 2011 effectively elevated these issues to the global stage, and much has been achieved in the five years since. This was the first act of NCDs becoming a full-fledged part of the global health agenda.

The second act is the subject of this book: how to apply our growing knowledge in ways that can slow the growing epidemic. The chapters in this book deal with the nuts and bolts of NCDs in developing countries: how to improve health outcomes in people living with a noncommunicable disease, as my colleagues Ken LaBresh and Kathy Lohr describe in the final chapter. It's slow and challenging work. Part of it is getting doctors to talk to their patients about lifestyle (Williams and LaBresh, chapter 6), improving diabetes medication adherence through better health literacy (Wald et al., chapter 4), searching for the reasons for a surge in chronic kidney disease (Redmon et al., chapter 7), and finding cancer before it becomes untreatable and unaffordable (Subramanian et al. and Krishnan et al., chapters 1 and 2). My colleagues worked with local communities and their health providers in creative ways to find solutions for the how as well as the what of NCDs. This is where the answers lie. Not in the halls of the UN—although the next General Assembly meeting on NCDs in 2018 will further advance the cause and the commitments to global NCDs—but with the researchers, the communities, the national governments, businesses, households, and funders who have come to care about preventing and controlling NCDs—not just to save lives, but to improve them while they last.

I am excited about the breadth of capacity at RTI International to address global NCDs and the deep commitment of the researchers and the institute itself to work with developing countries to find solutions for the growing threat to their well-being and economies. That is why I joined RTI this year as Vice President for Global NCDs, and why RTI will continue the kind of problem-solving described in this book.

There is far to go before the final act can be written. Governments need to meet their commitments made in New York, especially for financing NCD

prevention and control. Health systems need to shift from an acute care disease control model to a chronic health management model. And different sectors in society need to be unified on what creates societal well-being across many dimensions, with good health paramount.

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Preface

This book presents the results of seven pilot projects, funded by RTI International under an RTI Grand Challenge, to explore applications of RTI's expertise and global presence to reducing the burden from noncommunicable diseases (NCDs) and improving patient outcomes in low- and middle-income countries (LMICs).

The projects funded were to be exploratory in nature; thus, they represent a variety of approaches but were confined to one or more of the four NCDs responsible for the greatest impact on morbidity and mortality—cardiovascular disease, cancer, diabetes, and chronic respiratory diseases. As a requirement for funding, each project was required to work across disciplines within RTI as well as with partners from the target country.

RTI Grand Challenges have four general characteristics:

1. They target significant problems affecting humanity at large or at least on the scale of a nation.
2. They transcend the boundaries of scientific disciplines and political interests.
3. The problems addressed are perceived to be difficult and require significant efforts to execute.
4. Solutions to the problems are perceived to be achievable and have potential for substantial impact.

All four of these characteristics pertain to improving outcomes for NCDs in LMICs.

These RTI Grand Challenge projects were competitively funded for 18 months as pilot studies. The topics were developed in collaboration with in-country partners who could best leverage the combined expertise of RTI and local clinicians, hospitals, or clinics and other primary care settings, government officials, and others. The studies were intended to lay the groundwork for subsequent projects focused on NCD prevention, detection, treatment, and improved outcomes.

RTI is particularly well positioned to help improve outcomes for NCDs globally. This topic overlaps multiple core areas of expertise for which RTI is known internationally, and it represents our experience in the range of

disciplines required to address NCDs. In addition, RTI's expertise includes developing and assessing broad-scale interventions that have the potential to improve health outcomes among large groups of individuals.

Improving outcomes in NCDs in LMICs is a difficult endeavor that will require significant effort and collaboration. However, previous research and program implementation indicates that outcomes for NCDs can be improved. Given the tremendous impact of NCDs on morbidity, mortality, and health care costs worldwide, there is little doubt that efforts to improve NCD outcomes are a global health imperative and, indeed, essential to reduce the burden of NCDs on the world's populations.

The book is intended for potential international collaborators and funders. We believe that a better understanding of RTI's capabilities and collaboration expertise will lead to further partnerships based on RTI's growing presence around the world. This initial work in NCDs in LMICs will also provide the rationale for additional internal investment and collaboration at RTI. In these ways, we can enhance our ability to respond to this enormous global problem of NCDs and, in so doing, further RTI's mission of improving the human condition.

Kenneth A. LaBresh, MD

Introduction

Kenneth A. LaBresh and Michael T. Halpern

Background

Clinical and Epidemiological Issues

Noncommunicable diseases (NCDs), principally cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases, are the leading cause of death in the United States and worldwide. Approximately 62 percent of deaths worldwide (almost 36 million individuals annually) result from NCDs, with half of these patients (18 million) dying from cardiovascular diseases and 8 million dying from cancer.¹ In the United States, NCDs are responsible for 87 percent of deaths; a majority of these deaths are attributable to cardiovascular diseases (37 percent) and cancer (23 percent).^{2,3}

These conditions disproportionately affect low- and middle-income countries (LMICs). For example, 80 percent of various heart diseases occur in LMICs.¹ The risk of mortality between the ages of 30 and 70 from these disorders is highest in sub-Saharan Africa, Eastern Europe, and parts of Asia.²

Morbidity and mortality from NCDs are almost certain to increase over the next decades; they are also likely to affect LMICs disproportionately, with 80 percent of NCD-attributable deaths occurring in LMICs. Global NCD deaths are projected to increase by 33 percent by 2030; deaths from cardiovascular disease, the leading cause of death in all regions except sub-Saharan Africa, are estimated to rise from 17.1 million (2004) to 23.4 million deaths (2030). Cancer deaths will increase from 7.4 million to 11.8 million over the same period. With more than 1.1 billion adults overweight in 2010 (312 million of whom were obese), deaths from diabetes are expected to increase from 1.6 million to 2.4 million over the period 2015 to 2030. Already, 70 percent of the diabetes burden is borne by developing countries.³

In addition to the effects on morbidity and mortality, NCDs also have substantial economic impact. For example, the global cost of cancer in 2008 was estimated at \$895 billion, representing 1.5 percent of the world's gross domestic product (GDP).⁴ Rates of NCDs and associated costs will almost

certainly continue to increase. For instance, the direct cost of cardiovascular disease in the United States is expected to increase from \$273 billion in 2010 to \$818 billion in 2030.⁵ Over the next 20 years, NCDs worldwide are expected to cost more than \$47 trillion, representing 5 percent of 2010 global GDP. Nearly one-half of this cost, \$21 trillion, will affect LMICs.¹

Many of the morbidity, mortality, and costs associated with NCDs can be avoided. At least 40 percent of cancers and 80 percent of premature cardiovascular disease and diabetes could be prevented through smoking cessation, improved diets, and adequate physical activity.⁶ Tobacco use alone accounts for 1 in 6 deaths from NCDs.¹ In addition, changes to existing health care systems and development of new systems and strategies can improve treatment of NCDs and NCD risk factors. Such advances can lead to increased life expectancy, improve quality of life, and enhance functional status; they also have the potential to decrease health costs. However, to reduce exposure to NCD risk factors and improve diagnosis and treatment of NCDs, we need innovative interventions, programs, policies, and technologies on the individual, system, and societal levels.

Addressing Noncommunicable Diseases in Low- and Middle-Income Countries

In 2011, the United Nations General Assembly met to discuss a new international agenda for NCDs. This was only the second time the General Assembly had ever met to discuss a health issue (the first meeting was to discuss AIDS). The resolution adopted by the General Assembly at this meeting states that the representatives in attendance:

Acknowledge that the global burden and threat of non-communicable diseases constitutes one of the major challenges for development in the twenty-first century, which undermines social and economic development throughout the world and threatens the achievement of internationally agreed development goals.⁷

The resolution also states that the assembled representatives

Recognize the urgent need for greater measures at the global, regional and national levels to prevent and control non-communicable diseases in order to contribute to the full realization of the right of everyone to the highest attainable standard of physical and mental health.⁷

Directed at improving outcomes for NCDs, the World Health Organization (WHO) NCD Global Action Plan specifies six objectives:⁸

1. Raise the priority accorded to preventing and controlling NCDs in global, regional, and national agendas and to internationally agreed-upon development goals through strengthened international cooperation and advocacy.
2. Strengthen national capacity, leadership, governance, multisectoral action, and partnerships to accelerate country response for prevention and control of NCDs.
3. Reduce modifiable risk factors for NCDs and underlying social determinants by creating health-promoting environments.
4. Strengthen and orient health systems to address prevention and control of NCDs and the underlying social determinants through people-centered primary health care and universal health coverage.
5. Promote and support national capacity for high-quality research and development to prevent and control NCDs.
6. Monitor trends and determinants of NCDs and evaluate progress in their prevention and control.

As discussed by the *Lancet* NCD Action Group, interventions to address NCDs should meet rigorous, evidence-based criteria, have a substantial effect on health, be cost-effective, have low implementation costs, and be politically and financially feasible for scale-up.⁶

Pilot Projects Supported by the RTI International Grand Challenge

The studies that RTI International supported through this RTI Grand Challenge focused on

- understanding conditions, attitudes, and behaviors that affect the detection and progression of NCDs, so as to form a basis for interventions
- preventing development of or exposure to risk factors related to NCDs
identifying and treating risk factors related to NCDs
- diagnosing and treating NCDs
- implementing health care delivery changes to prevent the recurrence of NCDs.

Specifically, the seven studies presented in the following chapters were all performed in Asia, and all collaborated to varying degrees with local partners. They cover a range of approaches and NCD problems. They demonstrate the breadth of RTT's expertise and capabilities and illustrate how we developed relationships necessary to work in diverse cultures. As such, these pilot projects address WHO NCD Global Action Plan objectives 2, 3, and 5.

Two studies in India address the barriers to screening and treatment for oral cancers and for cervical cancer (Chapters 1 and 2). Patients with oral cancer frequently present with late-stage disease. Better screening and education for patients are seen as potential interventions to increase the likelihood of earlier detection. Tobacco regulation is also recognized as an important potential intervention. The project on cervical cancer screening found that providing patient educational handouts about the disorder and its risk factors, fostering encouragement from husbands to undergo screening, and enhancing the availability of screening were important steps for early detection and treatment. In both cancer-related projects, the social determinants of disease and risk play a central role.

The third study reports on the development of a microsimulation model to examine low birth weight and obesity in Indonesia (Chapter 3). This population forecasting model was intended to be used to project the potential results of various interventions to reduce stunting and low birth weight, which are associated with the development of obesity, and to forecast future rates of obesity in the general population. The results of such modeling could be used to inform health policy and play a role in addressing WHO NCD Global Action Plan objectives 2 and 5, with a view to expanding national capacity to reduce the underlying risk of multiple NCDs and providing a platform to model and predict risk factor development.

The next three studies focus on interventions to prevent and treat diabetes and stroke. The first of these studies (Chapter 4), carried out in India, evaluated the use of information technology to support health literacy and medication use in patients with diabetes. The study set out to examine how an internet-based program for producing patient handouts in the local language might be implemented in a primary care setting, and it attempted to document potential benefits of such medication information, the acceptability of such handouts for patients, the preferred source of these handouts (physicians, nurses, or pharmacists), and the knowledge of and adherence to medications to treat diabetes.

The next two studies both focus on stroke, which is the leading cause of mortality in China and Indonesia. The study in China sought to adapt the Get With The Guidelines (GWTG) program developed by the American Stroke Association to the environment of hospitals in China (Chapter 5). GWTG-Stroke was designed to assess and improve the acute treatment of stroke and the secondary prevention therapies that reduce death from subsequent stroke and myocardial infarction. A key element in supporting improvements in the quality of stroke care is acquisition of the clinical data elements that can be used to create evidence-based quality metrics. These measures can be used both to track clinical performance and support improvement of care delivery. The primary goal of this project was to use and integrate existing electronic data systems to collect data while minimizing the burden on clinicians.

In Indonesia, health workers carried out a stroke prevention intervention in four community health centers (*puskesmas*) (Chapter 6). The prevention program sought to prompt physicians and nurses to increase the frequency of patient assessment and counseling needed to reduce stroke risk factors. The study also measured the impact of the program on clinicians' discussions with patients about their stroke risk and recommendations to modify patients' risk factors. The intervention used in-depth interviews with the primary care physicians and nurses who conducted the intervention to learn how to improve the intervention and to overcome barriers to implementation encountered in the clinics.

The final project addresses the mystery surrounding the development of chronic kidney disease of unknown etiology in Sri Lanka (Chapter 7), which has become a major health challenge. Prior assessments of potential etiologies have been narrowly focused and have failed to identify fully explainable or defensible causes of this disorder in rural, dry areas of the country. Although this study also did not identify a clear, single etiology, it did document the likelihood that several environmental or behavioral risk factors play a role in the pathogenesis of this severe disorder. The team made several recommendations for more systematic, rigorous assessments, including advanced laboratory studies, for future analyses.

The conditions selected for study and various disease-specific interventions or programs were related to the major NCDs as defined by the *Lancet* NCD Action Group⁶ and the WHO Action Plan,⁸ with one exception. The problem of chronic kidney disease of unknown etiology in Sri Lanka has been an unsolved riddle affecting working-age men for some years (as it is in many

countries); those grappling with the problem sought RTI's assistance to assess more effectively the role of environmental toxins. Although the full spectrum of causes was not established, collaboration with RTI has led to the development of more sophisticated analytic methods to address the problem.

Going Forward

Researchers in the United States have demonstrated the ability to transform the delivery of care and prevent future cardiovascular events by facilitating system change at multiple points in the care delivery system.⁹⁻¹¹ Changing the systems of prevention and care delivery relies on the flexibility of the professionals delivering care, supported by expertise in system change.¹² Collaborative relationships among government leaders, policy makers, and health care professionals in the target LMICs are essential.

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Barriers to Screening, Diagnosis, and Treatment of Oral Cancers in India

Sujha Subramanian, Sonja Hoover, and Patrick Edwards

Introduction

Oral cancer is a significant cause of death worldwide. Low- and middle-income countries (LMICs) bear more than two-thirds of this burden. The most recent statistics from the World Health Organization indicate that Southeast Asia accounts for one-third of new oral cancer cases and 45 percent of deaths from it.¹ More than 100,000 oral cancers will be diagnosed annually in India alone²; unfortunately, 60 percent to 80 percent of these patients will present with advanced disease, as compared with 40 percent in high-income countries.³ In addition, even within India, patients with low socioeconomic status bear the brunt of the disease because they have a higher incidence rate.⁴

Oral cancer includes cancers of the mucosal lip, tongue, gum, floor of the mouth, palate, and mouth. The risk factors traditionally associated with oral cancers are tobacco use (smoking or chewing) and alcohol use. In recent years, however, cancers of the oropharynx have been associated with the presence of the human papillomavirus.⁵ Other risk factors may include family history and excessive exposure to the sun. Therefore, primary prevention is an important aspect of oral cancer control along with screening to detect cancers at an early stage when treatment is most effective.

Prior research has demonstrated that oral cancer screening using visual inspection by trained health workers can lower mortality and is cost-effective. A large randomized controlled trial of almost 192,000 individuals showed a significant reduction in mortality among those in the intervention arm receiving screening (29.9 cases per 100,000) versus those in the control arm who received only educational messages and usual care (45.4 cases per 100,000).⁶ The follow-on cost-effectiveness analysis reported an incremental cost per life-year saved of US \$835 overall and US \$156 for the high-risk population of those using tobacco or alcohol (or both).⁷ More

important, the analysis revealed that three cycles of visual inspection can be performed for less than US \$6 per person in India, suggesting that this approach can be implemented even in a limited resource setting, especially when targeted at high-risk individuals. These two studies published by the research team serve as the key body of evidence for oral cancer screening in LMICs.

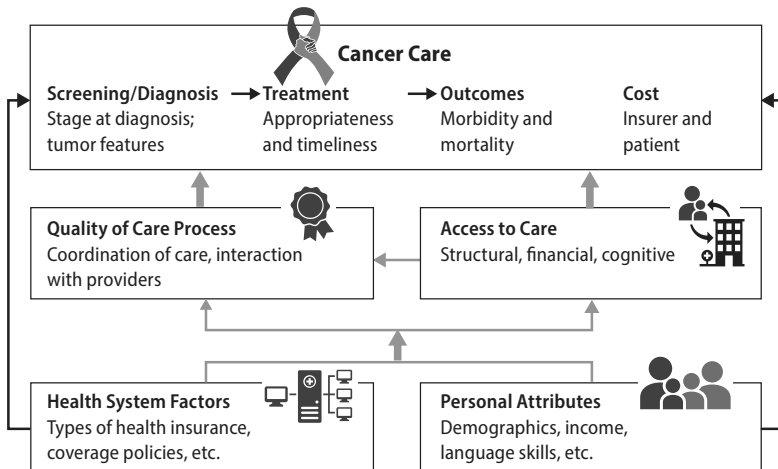
This chapter assesses barriers along the cancer care continuum to identify interventions that can be implemented to improve patient outcomes. In the oral cancer screening trial in the Trivandrum region, 5,145 individuals screened positive, but only 3,218 (63 percent) complied with follow-up diagnostic recommendations.⁶ Discussions with regional cancer center staff in India revealed that only about one-half of the oral cancer patients complete treatment. Low compliance with oral cancer care recommendations is a significant issue that needs to be addressed to improve outcomes. Therefore, assessing barriers at the individual, provider, and system levels is an essential first step.

Methods

Conceptual Framework

For the analyses, we obtained both quantitative and qualitative information to identify the most promising interventions to decrease the burden from oral cancers. Figure 1.1 describes the framework we used to guide the data

Figure 1.1 RTI conceptual model to assess barriers to cancer care

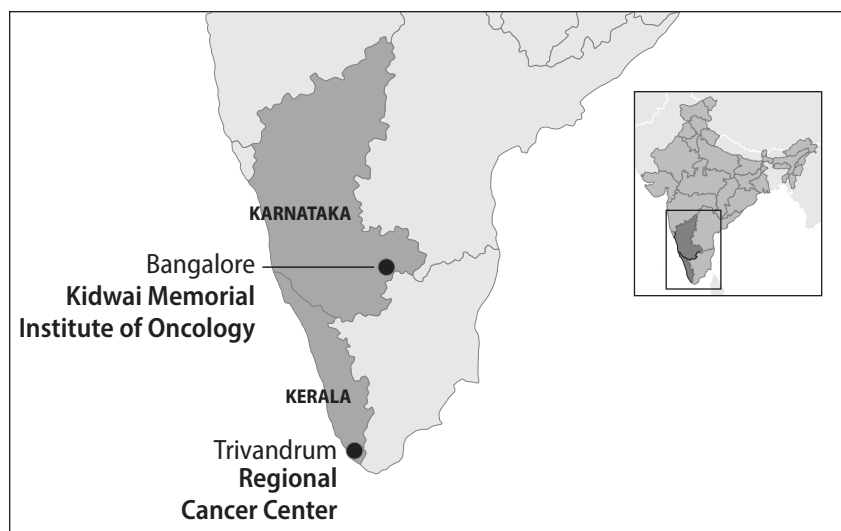


collection and analysis. Patient characteristics and health system factors (e.g., insurance coverage is increasing in India) can affect access to care and quality-of-care processes. Decreased access to care includes structural barriers (e.g., access to providers), financial considerations (e.g., ability to pay for travel to seek care), and cognitive factors (e.g., understanding of treatment recommendations). Quality-of-care process measures include a variety of factors, such as coordination of care and interaction with providers. We also included health outcomes as measures of the quality of care, presented here in the cancer care continuum.

Research Partners

We partnered with two cancer centers in India: the Regional Cancer Center in Trivandrum City and the Kidwai Memorial Institute of Oncology in Bangalore (see Figure 1.2). The cancer centers offer care free to the poor and at a reasonable charge to those at higher income levels. Both centers provide oral cancer care in a specialty clinic to more than 1,000 oral cancer patients annually. The International Agency for Research on Cancer ran a decade-long screening trial for oral cancers in Trivandrum district. Therefore, we hypothesized that patients in Trivandrum district would be more aware of

Figure 1.2 Intervention and control clusters in the oral cancer clinical trial in Trivandrum City (Regional Cancer Center) and Bangalore (Kidwai Memorial Institute of Oncology)



oral cancer risk factors and better informed about cancer screening than the patients in the Bangalore area.

Data Collection

We collected data from several different sources. One source was a patient survey; Figure 1.1 outlines the conceptual model of the survey. The survey instrument included questions in the following domains: patient demographics and behaviors; knowledge and attitude regarding oral cancer risk factors and treatment; access to care; health-seeking behavior; treatment and survivorship; and barriers. We pretested the survey with five representative patients at each site and then administered it via face-to-face interviews with patients recently diagnosed with oral cancer. The staff from the two cancer centers interviewed 200 patients each (for a total of 400 patients) using a consistent protocol.

The remaining source of data consisted of two focus groups with 12 nurses and social workers from the Kidwai Memorial Institute of Oncology in Bangalore. The first group consisted of seven experienced nurses who generally each had more than 10 years of work experience and an average of about 3 years working directly with oral cancer patients. The second group included five social workers who each had an average of 25 years of experience in cancer care. We used open-ended interview questions to understand interviewee perception of patient barriers and explore approaches to reduce the identified barriers.

Results

Findings from the Patient Survey

A total of 400 patients, 200 from each study site, completed the survey. The main findings are as follows:

- Patients with higher education are more likely to report accurately the risk factors for oral cancer and more likely to know about oral cancer screening.
- Patients receiving care at the Regional Cancer Center in Trivandrum City, who were likely exposed to the education messages from the decade-long clinical trial, consistently reported higher levels of knowledge about oral cancer than those receiving treatment at Kidwai Memorial Institute of Oncology.
- Even in the highest educated group, only two-thirds of the patients were correctly informed about oral cancer risk factors and screening.

Respondents reported considerable financial barriers related to treatment, transportation, and the need to stay near the hospital to undergo treatment. The detailed findings from the patient survey are reported elsewhere.⁸

Findings from the Focus Groups

The barriers identified in the focus groups fell into two categories: (1) patient barriers and (2) institution or health system barriers. Table 1.1 summarizes these barriers and suggested interventions; we discuss the points in more detail in the sections that follow.

Patient Barriers

Financial Barriers. The population that Kidwai Memorial Institute of Oncology treats is very poor, with low levels of education. The patients tend to be day workers or farmers, with unstable and variable incomes. The interviewees estimated that patients earn less than 1,000 Indian rupees per month, which is approximately US \$16. Given the extreme poverty of the patients, being diagnosed with cancer creates a great burden.

Patients can choose the type of hospital where they will be treated; however, according to interviewees, private hospitals are more expensive than the regional cancer centers. Government programs are in place to assist patients financially, but costs associated with treatment remain. These include costs of surgery, postoperative care, and medications. In some cases, patients need to go through multiple surgeries. According to one nurse, “As long as [the patients] are in the hospital, they take medicines ... but when they go back to their villages, they may not want to spend the money to buy the medicines, or those medicines may not be available in their village.”

Additional costs arise for travel and lodging—for family members as well as for patients. Patients must take time from work for treatment and may risk losing their jobs if they are away too long for treatment or for repeated hospital stays. Finances become even more difficult when the patient is the primary earner for the family. One social worker commented that “patients often sell

Table 1.1 Barriers and suggested interventions

Patient Barriers

- Financial
- Lack of education
- Stigma and fear

System Barriers

- Shortage of facilities
- Shortage of staff
- Patients' use of traditional healers and Ayurvedic hospitals

Suggested Interventions

- Price increase on tobacco products and taxes
 - Education of population, health workers, and traditional healers
 - Improvements in existing facilities
-

their land and jewelry in order to meet treatment costs.” Because of the lack of finances, patients may forgo follow-up care and treatment, which can result in recurrence of the cancer. The interviewees indicated that with financial help, patients are more likely to follow up with postoperative care.

Education. As we noted previously, patients residing in the Kidwai area have very low levels of education and literacy. Because of this, teaching patients about the importance of prevention, screening, and treatment is difficult. Patients may not understand why prevention is important (e.g., why they should quit using tobacco products) and may not recognize the symptoms of oral cancer when they appear. Teaching them about postoperative care may also be difficult. According to one social worker interviewed, “Patients face most problems postoperatively, as many have lost a part of their mouth, like [the] tongue, and are not able to talk or eat...” Patients also must learn to become diligent in taking any prescription medications as adherence is often low.

Another issue that follows from low education levels is that patients may not give much priority to their own health care. Persons tend to present with oral cancer at a later stage of the disease because they defer screening (or visiting a doctor generally) for work, caretaking of others, and familial obligations.

Stigma and Fear. The interviewees noted the great amount of stigma and fear among the patients, particularly among those who reside in rural areas. Surgery for oral cancer can lead to disfigurement, because of losing part of the mouth or tongue, which can further lead to the inability to talk or eat. Some consequences of improper postoperative care can arise, such as foul mouth odor and even the development of maggots in the mouth. These sequelae can all lead to social isolation for the patient.

Interviewees reported that patients experience a range of emotions, including depression and anxiety, because of the cancer. Lack of support from family and friends can compound these problems. Patients fear rejection and need assistance after the surgery. The interviewees have seen unsupportive family members who do not know how to change dressings and who do not bring patients back for follow-up treatment.

“Most of the oral cancer patients are elderly,” according to one social worker, “and may not have any family support during their illness even though they face several problems like not being able to eat or swallow.”

Further, community beliefs can ostracize the patient. Some believe that cancer is caused by past sins, it is a curse, or it is communicable or contagious. Some interviewees said that these were all reasons for patients to forgo early detection in the event that they do have cancer. However, some interviewees indicated that outreach and education has helped to reduce stigma.

Institutional and Health System Barriers

Shortages of Facilities and Staff. In India, the government partially funds 27 regional cancer centers. Kidwai is one of them, and it serves approximately 1,000 patients annually in its oral cancer clinic. However, the oral cancer clinic at the hospital has only three staff physicians to support the oral cancer caseload: a professor, an associate professor, and an assistant professor. According to the interviewees, the staff physicians perform between four and five surgeries per day, some major and some minor. In addition, these physicians perform additional, nonmedical roles including administrative functions and counseling; these duties all take time away from their medical roles. Patients often have to wait several hours to receive care because of the limited number of staff.

The 12 interviewees indicated the need for more staff, particularly counselors and social workers. Patients require support both before and after their surgeries, but many do not receive it from physicians, nurses, or family and friends. Physicians, because of large caseloads, do not have the time to spend with patients. One nurse commented that “the doctors don’t ... spend sufficient time with [patients] since Kidwai is a government hospital and is overcrowded.” Although nurses try to provide counseling, many do not have the time or the background to do so. In addition, although social workers provide counseling, many physicians do not refer patients to them because they believe that the social workers do not have the proper educational background for it. Moreover, although the social workers do attempt to help, their time is divided among different tasks, including providing information on financial assistance.

Nurses also discussed poor morale. In addition to being overworked and doing nonmedical tasks, the nurses feel underappreciated, because they do not receive the same level of acknowledgment of their contributions as physicians. The nurses indicated that they “don’t mind doing the work and helping patients, but their work should be appreciated and they should be given timely incentives and promotions.”

Use of Traditional Healers. The interviewees also indicated that patients are influenced by the advertisements of traditional healers that promise to cure their conditions. These include homeopathic clinicians and other types of healers. Patients may opt for these modalities because the practitioners are local and the waiting times are shorter.

However, many of these practitioners have not been formally trained in how to screen and treat cancer. By the time patients who have not been cured present at Kidwai, their cancer is at a later stage and more difficult to treat. Often, the cancer is at a terminal stage, and only palliative care can be offered.

Suggested Interventions

The nurses and social workers had several broad suggestions to facilitate cancer prevention and treatment. They recommended that the government either ban tobacco products outright or increase the tax rate on or the price of tobacco products to discourage purchase and use. They pointed to the banning of gutka, a tobacco product, as an example of government involvement.

They also believed that broad-based oral cancer education and awareness campaigns are needed. This is particularly important because they are observing higher rates of smoking across all age groups, especially among younger and educated people. Interviewees thought that such campaigns could be done through mass media and cancer detection camps. Cancer detection camp teams conduct small-group educational sessions in hospitals and communities across the state. The workers are considered well versed in approaching and educating the community. Some cancer detection camps are mobile units that are equipped to screen and refer patients for treatment.

Interviewees further recommended education of health providers, particularly in rural areas, including traditional healers. Often, patients are not referred to cancer centers quickly enough because the cancer is not identified; even if cancer is identified, patients are treated with alternative therapies (e.g., homeopathy or Ayurveda). If patients present at a treatment center, the cancer is at a later stage, and so curative treatments cannot be provided. Providers and healers need to be educated about the importance of referring patients to cancer centers immediately upon diagnosis so that patients can begin treatment.

Discussion

The findings from the patient survey and focus groups indicated numerous barriers along the continuum of cancer care. Better knowledge of cancer risk factors might motivate individuals to change their behaviors concerning use of tobacco and alcohol. In addition, information on the symptoms of oral cancer and easier availability of screening may motivate more individuals to seek care earlier. Education of providers, including physicians, nurses, and social workers, is an important component of any education campaign. Interventions to improve patient and provider knowledge can help shift the diagnosis to an earlier stage. Integrated delivery of education and screening with other cancers and noncommunicable diseases could provide an efficient approach to address multiple diseases with shared risk factors.

Patients diagnosed with oral cancer face many barriers, even though low-cost or free treatment is available. The regional cancer centers may be overwhelmed by the numbers of cases that need to be treated; which can lead to long wait times and limited face time with the medical staff. Resources allocated to the regional cancer center should be thoroughly assessed to ensure that staffing levels and funding are adequate for the volume of patients treated.

Patients, especially in rural areas, may face significant expenses traveling and staying near the cancer center to receive care. In addition, they may

Key Findings and Lessons Learned

- Systematically assessing facilitators and barriers from the patient perspective is important.
- Support medical staff, including nurses and social workers, often receive information directly from the patient and, therefore, can provide valuable feedback to improve patient experience.
- Even when cancer treatment is subsidized or free, patients face substantial economic burden related to travel to regional centers to receive care.
- Specialty care is available only in tertiary care centers, which can result in substantial economic barriers related to travel time and cost. Serious consideration should be given to ensuring that at least certain levels of treatment related to noncommunicable diseases are available in more geographically dispersed settings.
- The lessons learned in this study on oral cancer care generally apply to other noncommunicable diseases in low- and middle-income countries. Greater emphasis on early detection and more patient-friendly treatment services can make tremendous inroads in reducing the noncommunicable disease burden.

not have the financial means to follow through with post-treatment recommendations. Approaches to minimize the financial burden may increase treatment compliance.

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Addressing the Challenge of Cervical Cancer Screening: Foundational Work in Karnataka, India

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Introduction

Burden of Cervical Cancer

Cervical cancer is a leading cause of cancer-related morbidity and mortality among women in India. In 2012, more than 120,000 women were diagnosed with cervical cancer in India, corresponding to an age-standardized incidence rate of 22 per 100,000.¹ According to the World Health Organization (WHO), the annual burden of new cases in India will increase to nearly 225,000 by 2025 at current incidence rates and in the absence of systematic prevention efforts.²

The considerable burden of cervical cancer in India persists despite the fact that effective primary and secondary prevention tools, namely vaccination against human papilloma viruses and screening and treatment, exist. In fact, WHO considers screening and treatment of precancerous lesions to prevent cervical cancer to be a “best buy” intervention.³ Numerous studies across India have demonstrated the feasibility and acceptability of cervical cancer screening and its effectiveness in reducing morbidity, promoting early detection, and preventing premature mortality.⁴⁻⁶ However, few large-scale organized screening programs have been established, and most women continue to be diagnosed at advanced stages with poor prognosis.⁷

Research and programmatic experiences in India have highlighted implementation-related challenges that need to be addressed for effective large-scale cervical cancer prevention.⁸ For example, recruiting large numbers of women to participate in screening and ensuring follow-up of women who require additional monitoring, testing, or treatment have both been difficult. In fact, a review of cervical cancer screening programs in low- and middle-income countries (LMICs) found India to have the lowest

rate of participation.⁹ Randomized controlled trials that used comprehensive mobilization efforts have been successful in meeting recruitment targets; these strategies include health education, personal invitations by providers and community members, clinics in close proximity to women, and treatment offered during the same session as screening.¹⁰ However, this broad approach has not been consistently successful in achieving high screening uptake⁵ or adherence to follow-up recommendations.¹¹ Thus, we need a comprehensive understanding of the factors that help or hinder the uptake of cervical cancer screening and follow-up services.

Study Objectives

Our foundational study addressed this need in two ways: (1) a review of the literature on cervical cancer screening and follow-up experiences in LMICs and (2) a qualitative study in two rural districts in the southern Indian state of Karnataka. We had three main objectives. First, guided by the social-ecological theory of behavior, we aimed to examine the evidence on factors that facilitated or posed barriers to cervical cancer screening and follow-up across LMICs and to conduct additional research to examine factors specifically relevant in the Indian context. Second, using our literature review and formative study in India, we intended to propose a social-ecological model to depict how multilevel contextual factors influenced women's participation in screening and follow-up. Finally, we planned to use this conceptual model to guide identification of interventions to improve cervical cancer screening and follow-up implementation in India.

Methods

Project Team and Setting

Our project drew on RTI's multidisciplinary expertise and research partnerships and infrastructure in India. A transnational team with training and experience in social and behavioral science research, medicine, and health promotion conducted the study. The team included US- and India-based RTI staff, consultants who were part of RTI's collaborative research program in India, and three undergraduate research interns (one of whom later joined the RTI staff).

RTI partnered with Cancer Care India, a nongovernmental organization focused on cervical cancer prevention in Karnataka, to conduct the qualitative data collection. The principal investigator of the study was based in Karnataka;

at the time we did this pilot study, she was also providing technical assistance to the state government to design, implement, and evaluate a cervical cancer screening and treatment initiative. Insights from this project helped shape the study objectives and methods.

We carried out the qualitative study in two predominantly rural districts of Karnataka: Bangalore Rural (population of 990,923 in 2011) and Chikkaballapura (population of 1,255,104 in 2011) at a distance of 50 to 150 kilometers from Bengaluru, the capital city. Data from the Population Based Cancer Registries indicated that, between 1990 and 2011, the age-adjusted rate of cervical cancer in urban Bengaluru was 18.9 per 100,000.¹² From 2007 to 2011, cervical cancer comprised nearly 28 percent of all cancers among women recorded by the Hospital Based Cancer Registry in Bengaluru, and it was the most common cancer in women.¹³ Although breast cancer has overtaken cervical cancer as the leading cancer among women in the Bengaluru Hospital Based Cancer Registry in the post-2011 period, morbidity and mortality caused by cervical cancer remain substantial (Dr. Chaluvarayaswamy Ramesh, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India, personal communication, November 2014).

Our partner, Cancer Care India, has been promoting cervical cancer prevention in rural and urban communities, including in Bangalore Rural and Chikkaballapura districts, in Karnataka. Their prevention program includes education of screening-eligible women (ages 30 to 60 years) by community leaders and health workers about the benefits of a comprehensive health examination; these activities are followed by Pap smear-based screening through camps run by a social worker and a physician employed by the organization. Women who screen positive are informed about their result with the help of local community health workers, and they are offered facilitated referrals to diagnostic and treatment services provided by governmental or private clinics and hospitals.

Theoretical Framework

The socio-ecological theory of behavior guided our project.¹⁴⁻¹⁶ This theory proposes a range of factors operating at the levels of the individual, family, community, and health care system that shape an individual's health behaviors. When applied to cervical cancer screening and follow-up, this theory encourages an examination of how individual knowledge and beliefs,

family relationships, community norms and perceptions, and health care organizational characteristics influence all these processes.

Literature Review

Building on a review of cervical cancer screening research and programmatic experiences in India,¹⁷ we developed a protocol to review evidence on factors that influenced screening uptake and follow-up across LMICs. Our review of the Indian literature revealed that most studies on this issue lacked theoretical grounding and focused on a narrow set of potential facilitators and barriers. Thus, we decided to conduct a more comprehensive narrative review and also to examine how the social-ecological theory of behavior would promote an understanding of the range of potential factors that may influence the success of cervical cancer screening efforts.

We used the following standard five-step process to implement our review:

1. Develop key questions for the review and study inclusion and exclusion criteria.
2. Identify search terms and conduct an electronic literature search using major databases such as Medline, ISI Web of Science, and the Alliance for Cervical Cancer Prevention (ACCP).
3. Review titles and abstracts produced in the searches against inclusion/exclusion criteria.
4. Retrieve full-text articles for “included” citations.
5. Review and abstract key data from all retained articles using an abstraction form.

The four key questions (KQs) for our review focused on the facilitators and barriers to cervical cancer screening (KQs 1 and 2) and post-screening follow-up (KQs 3 and 4). We focused on the four levels of actors (i.e., individual, family, community, and health care system).

We included studies that were English language, peer reviewed, and published or in publication between January 1, 2003, and May 31, 2013. Included studies were limited to women eligible for cervical cancer screening based on age and presence of a cervix; they had to have been conducted in LMICs in Asia, Latin America, and Africa according to the World Bank definition and categorization.¹⁸ Studies were eligible if they examined cervical cancer screening behavior and knowledge, attitudes, or beliefs. We included

a broad range of study designs because the goal was to identify the breadth of factors related to screening uptake and follow-up that had been examined. We did not limit or select studies based on the rigor of their design or study methods.

We defined search terms through an iterative process. We identified a total of 191 articles and revised the abstracts for inclusion. Of these, 38 articles, reporting on 29 unique studies, met our inclusion criteria and were retained for abstraction. We ascertained the following information from selected articles: study design and methods, country, population, outcomes, and facilitators of or barriers to cervical cancer screening and follow-up. We then synthesized these data within the context of our theoretical framework.

Qualitative Study

Study Population

We conducted the qualitative study in two rural districts: Bangalore Rural and Chikkaballapura in Karnataka State. Our partner, Cancer Care India, purposively selected the villages to include both those that had been exposed to its cancer prevention education and screening efforts and those that had not yet been exposed.

The Institutional Review Board at RTI International reviewed and approved our protocols and instruments. We obtained written informed consent from all study participants.

Data were gathered from a range of stakeholders in the community. These included women who were in the screening-eligible age group of 30 to 60 years, husbands of women in this age group, community health workers (e.g., physicians employed at local primary health centers, frontline health promoters called ASHAs [accredited social health activists], day care workers) and community leaders (e.g., members of the village government, women's self-help group members).

Data Collection: Focus Groups and Interviews

We conducted three main data collection efforts: (1) focus group discussions with women and men (husbands) in the community; (2) individual or small group (two or three individuals) interviews with community leaders and health workers; and (3) individual interviews with women who had undergone cervical cancer screening. To steer the discussions and interviews, we developed a semi-structured guide based on our conceptual framework and the literature review, keeping in mind the challenges of translating questions

into the local language, Kannada. For example, given that we anticipated very low levels of awareness about cervical cancer and screening, we needed to use extremely simple terms to explore the study populations' perspectives on screening through a gynecological examination. Because communities are aware of "uterus examinations" in the context of pregnancy, we used this terminology to explore factors that would influence women's willingness to undergo screening. We developed discussion guides in English and translated them into Kannada. The India- and US-based investigators reviewed drafts and refined them iteratively.

Participants from villages where Cancer Care India had conducted cervical cancer screening programs were asked questions in several domains. These domains included understanding and perceptions of cervical cancer and screening; ways in which they received messages about cervical cancer and screening; and factors that influenced their decision to undergo screening. Interviews focused on ascertaining the factors that supported women in obtaining screening and what their screening experiences had been. We also interviewed participants from villages where cervical cancer screening programs had not been conducted. In those villages, we explored participants' willingness and motivations to participate in screening; the type of information they desired; how information could be disseminated in the community; and where and how screening services should be offered.

Because of differences in the views and experiences of women in different age groups, in particular differences in power dynamics that may be age-related, we conducted focus group discussions with women grouped by age (30–45 years and 46–60 years).

The research team provided information about the study to recruited individuals using a written informed consent form. Those who were willing to participate provided written consent. Interviews and group discussions took place in the village—at schools, health centers, or day care centers. A team experienced in conducting qualitative research on women's health issues, including a clinician, carried out the interviews. We also collected sociodemographic data from participants. We recorded the discussions and interviews, and a professional translator translated and transcribed them. A member of the research team reviewed the translated transcripts for accuracy.

Analyses

We conducted a thematic analysis of the qualitative data. This involved reading the transcripts several times to become familiar with the content. We

developed a list of codes based on key themes (such as cancer awareness, fear of cancer, importance of quality of care). We used Atlas.ti software for coding and analysis.¹⁹ Two members of the team coded the transcripts.

We then analyzed the coded data to summarize key themes and to explore data by the levels of the socio-ecological model. We also examined different stakeholders' perspectives on each theme to identify key factors that appeared to influence cervical cancer screening and follow-up.

Results

The appendix table at the end of this chapter describes the 29 unique studies (38 articles) from our review of this literature. Findings from these studies are incorporated in our discussion. In addition, a total of 147 individuals participated in our qualitative study: 81 women in the screening-eligible age group, 39 husbands, 11 community leaders, 10 health care workers, and 6 women who had undergone cervical cancer screening. In this section, we summarize our findings organized by the social-ecological framework.

Individual-Level Facilitators and Barriers

Several individual-level factors emerged as important in the literature review and our qualitative study. Across LMICs, studies consistently found that knowledge about cervical cancer screening was an important determinant of screening uptake and follow-up. Knowledge about the benefits of screening and the treatability of cervical cancer when detected early appeared to be key. Women's perception of susceptibility, a family history of cervical cancer, and perceived severity of the disease and its impact on reproductive health (particularly, fertility) and sexual duties were associated with screening intentions or behaviors. Similarly, our qualitative study found that women's awareness of cervical cancer, understanding of the benefits of screening, and knowledge of someone affected by the disease—coupled with a recognition of the value of staying healthy—motivated them to undergo screening.

Not surprisingly, the literature review found that lack of knowledge, misconceptions about cancer, and fear of the disease and of treatment were important barriers to screening and follow-up. For example, one study found that fear of being diagnosed as having cancer was associated with not being screened; in another, concern that screening would lead to worry was a barrier. Our qualitative study yielded similar findings. For instance, shyness was identified as a barrier to screening; however, being embarrassed and

therefore reluctant to be examined could be overcome by greater knowledge of the benefits of screening. A fatalistic attitude about illness—the notion that contracting a disease is a predetermined part of one's fate and must be faced as such—was also a hindrance to follow-up.

Household- and Community-Level Facilitators and Barriers

Studies found that husbands' support for reproductive health or cervical cancer screening was important. Several studies also suggested the importance of support of friends who had undergone or recommended screening and of being able to attend screening with friends. Our field research also highlighted the benefits of engaging husbands to promote screening among women: in villages where Cancer Care India had conducted education and screening programs, both men and women were in favor of screening. Men talked about actively encouraging their wives. We also found that women who had undergone screening were promoting screening uptake enthusiastically to other women in their community.

Several studies included in the literature review reported that lack of family and social support was an important barrier. This was especially true for husbands' support. Husbands' lack of support could be attributed to discomfort with male health care providers or misconceptions about screening or treatment. Participants in our qualitative study noted that husbands were more comfortable when female health care providers were offering the service.

Health System—Level Facilitators and Barriers

Both the literature and our qualitative study identified health system characteristics as important factors. The screening setting was particularly relevant—whether the setting was accessible, was affordable, and offered privacy and confidentiality. In addition, studies reported that women preferred female health care providers. These results were echoed in our qualitative study. A few studies noted that community educators encouraged women to go to mobile screenings and that community advocacy teams could increase women's participation. Women's groups, churches, and HIV voluntary counseling and testing centers were also used to promote services, as were television, radio, and street plays. From our qualitative analysis, we found that recommendations of screening by women who had used the service was the most important form of advocacy at the community level.

Inaccessibility and unaffordability of services were frequently mentioned barriers in the literature. Logistical factors such as long waiting times, needing

to travel long distances, and infrequent availability of services were clear barriers to follow-up and treatment. A few studies also reported barriers to treating including needing to make multiple clinic visits and not having access to high-quality providers (preferably female).

A few studies noted negative staff attitudes and behaviors and inadequate messaging about the importance of screening. In our qualitative project, participants repeatedly emphasized health systems barriers. In particular, they cited rudeness of health care providers, poor organization of services, lack of confidentiality, cost of services, and inaccessibility for working women.

Finally, participants in our qualitative study also highlighted fear of community gossip and a culture of silence around women's gynecological health as barriers to women coming forward to be screened.

Discussion

Key Findings

We identified a wide range of factors influencing cervical cancer screening and follow-up that can be organized using the social-ecological model to understand facilitators and barriers. Each of the levels of this model—the individual, family, community, and health care system—appeared to have a strong influence on these activities. The studies we reviewed and our qualitative research did not explore the relative influence of factors operating at these levels. In fact, the social-ecological model suggests that these levels are interdependent and have mutually reinforcing influences on individual behaviors and health outcomes.

Promoting cervical cancer prevention through screening, early detection, and treatment of precancerous and cancerous lesions is an important priority in India, which bears nearly 25 percent of the global burden of cervical cancer. Our research suggests that, in India and other LMICs, screening initiatives should pay attention to multilevel contextual factors in design and implementation. Indeed, our data suggest that screening programs should encompass a range of strategies that address multilevel influencers of service uptake. Interventions that simultaneously address factors operating at multiple levels are likely to have greater impact than strategies focused on any single level.

Our findings point especially to the importance of behavior and social change communication about cervical cancer screening and follow-up. Communication efforts should address individuals, families, communities, and

the health care system. Women and their families, especially husbands, should be knowledgeable about cervical cancer; they need to grasp who is at risk, what screening entails, and what the benefits are of screening, early detection, and treatment. Community leaders and health workers should be made similarly aware and recruited to promote screening. Health care providers, too, need to be educated and sensitized about women's needs, and care should be provided in a respectful, private, and confidential manner. In summary, communication efforts should take a "whole-of-family, whole-of-community" approach.²⁰

Community-level strategies should address the culture of silence that surrounds women's health and reduce the fear associated with cancer. This may be accomplished through programs that offer greater visibility to cancer survivors. Given that women (including health workers) in our qualitative study who underwent screening appeared then to be active promoters of the service, programs might consider initially offering screening to community leaders and health workers. Such an approach, which a pilot project led by the National Institute of Cancer Prevention Research is now following, may not only mobilize them to promote screening but also increase women's and families' confidence in the program.

At the health care system level, programs may need to address several factors. Our data underscore the critical importance of ensuring that female health care providers are available to conduct screening. The state of Tamil Nadu in India is already pursuing this approach; the program deploys female nurses to conduct screening at the primary health care level. Screening services should be well organized. For example, the registration process should be transparent, and waiting times should be minimal. Services should be free or at low cost, especially for poor women. Access to health insurance, particularly for diagnostic testing and treatment, can promote follow-up. Finally, screening should be in an accessible and convenient location—either in the village or at a primary health center. As participants in our qualitative study emphasized, services should be women-centered (responding to their concerns and needs) and of high quality.

Implications for Programs and Research

Given the substantial burden of cervical cancer in India, scaling up comprehensive prevention efforts across the country is imperative. As WHO recommends, a comprehensive prevention effort would involve offering human papillomavirus (HPV) vaccination to girls aged 9 to 13 years and screening and follow-up services to women aged 30 to 49 years.²¹ As our research

suggests, screening initiatives in India should focus on using evidence-based strategic communication about behavior and social change to promote prevention, engaging families and communities, and ensuring that health care organization and delivery are responsive to women's needs.

At the same time, we recommend conducting research simultaneously focused on understanding the acceptability and effectiveness of strategies that emphasize communication and on clarifying health care organization and delivery. Well-designed, rigorous investigations of the implementation of cervical cancer screening programs, including process and outcome evaluations, will further expand the evidence base for what works in LMIC contexts. Development of validated scales to measure cervical cancer-related knowledge, fear, and stigma is critical to assessing program outcomes and impact. More broadly, future research should draw on the implementation science research toolkit, including program implementation designs that allow for rigorous testing of strategies.

Conclusions

Cervical cancer prevention and control has recently grabbed the headlines in India, with the prime minister calling for the development of a national cancer screening framework and the launch of a program within the 2016–17 financial year.²² Such a program should draw on the existing evidence that points to a comprehensive, women-centered approach to screening and treatment.

Drawing on the insights from our literature review and qualitative study, RTI hosted a high-level symposium on catalyzing cancer prevention in India in 2015.²³ In addition, we are engaging in research to develop multilevel interventions involving communication about behavior and social change to advance comprehensive cervical cancer prevention and control, and we are creating tools to measure and evaluate the impact of such interventions. As part of this research, we are working closely with Indian state governments, cancer institutes, and global and national or local nongovernmental organizations. Many more such efforts can generate the much-needed evidence about what works to prevent morbidity and mortality caused by cervical cancer in India.

Key Findings and Lessons Learned

- A range of factors operating at the levels of the individual, family, community, and health system facilitate or pose barriers to cervical cancer screening and follow-up.
- Women's knowledge about cervical cancer and disease prevention, perception of susceptibility, family history of cervical cancer, and perceived severity of the disease were associated with screening intentions or behaviors.
- Lack of husbands' support because of misconceptions about screening or treatment or other factors (e.g., sex of the health care provider) was a barrier.
- Being able to go for screening with friends or having a friend who had undergone screening was a facilitator.
- At the health systems level, offering private, respectful, and confidential screening by female health care providers was key to promoting service utilization.

Appendix

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up

Author and reference	Study title	Country	Study design	Study population	Key question
Adamu et al. ²⁴	The effect of health education on the knowledge, attitude, and uptake of free Pap smear among female teachers in Birnin-Kebbi, North-Western Nigeria	Nigeria	Quasi-experimental pre-post	200 female secondary school teachers	KQ1–2
Agurto et al. ²⁵	Perceived barriers and benefits to cervical cancer screening in Latin America	Venezuela, Ecuador, Mexico, El Salvador, Peru	FG, IDI	46 IDIs and 16 FGs women aged 25–65; 10 IDIs and 3 FGs men; and 32 IDIs and 1 FG health care providers	KQ1–2, 4
Allahverdipour et al. ²⁶	Perceptions of cervical cancer threat, benefits, and barriers of pap smear screening programs for women in Iran	Iran	Cross-sectional survey	333 married women aged 15–49	KQ1–2
Al-Naggar et al. ²⁷	Knowledge and barriers toward cervical cancer screening among young women in Malaysia	Malaysia	Cross-sectional survey	287 female students	KQ1–2
Ansink et al. ²⁸	Cervical cancer in Bangladesh: community perceptions of cervical cancer and cervical cancer screening	Bangladesh	FG	220 women (aged 20–49) and men	KQ1–2

(continued)

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up (continued)

Author and reference	Study title	Country	Study design	Study population	Key question
Aswathy et al. ²⁹	Cervical cancer screening: current knowledge and practice among women in a rural population of Kerala, India	India	Cross-sectional survey	809 women	KQ1–2
Augusto et al. ³⁰	Barriers to cervical cancer screening in women attending the family medical program in Niteroí, Rio de Janeiro	Brazil	Cross-sectional survey with a prospective component	351 women who were referred to the Family Medical Program (public health program)	KQ2
Basu et al. ³¹	Women's perspectives on cervical screening and treatment in developing countries: experiences with new technologies and service delivery strategies	Low- and middle-income countries	Review	Women aged 25–65 covered by different studies	KQ1–2
Bradley et al. ³²	Women's perspectives on cervical screening and treatment in developing countries: experiences with new technologies and service delivery strategies	Low- and middle-income countries	Review	Women aged 25–65 covered by different studies	KQ1–2
Bradley et al. ³³	Widening the cervical cancer screening net in a South African township: who are the underserved?	South Africa	Cross-sectional survey	644 women aged 35–65	KQ1–2

(continued)

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up (continued)

Author and reference	Study title	Country	Study design	Study population	Key question
Donta et al. ³⁴	Awareness of cervical cancer among couples in a slum area of Mumbai	India	Cross-sectional survey	1,958 women aged 18–49 and their husbands	KQ2
Duran ³⁵	Examination with the health belief model of women's attitudes to cervical cancer and early diagnosis in Turkey: a qualitative study	Turkey	FG, IDI	11 onscreened, married women aged 15–49	KQ1–2
Farooqui et al. ³⁶	A qualitative exploration of Malaysian cancer patients' perceptions of cancer screening	Malaysia	FG, IDI	20 cancer patients aged 18–70 from oncology ward	KQ1–2
Gu et al. ³⁷	The influence of knowledge and perception of the risk of cervical cancer on screening behavior in mainland Chinese women	China	Cross-sectional survey	167 women (79 non-screened, 88 screened)	KQ1–2
Gu et al. ³⁸	Chinese women's motivation to receive future screening: the role of social-demographic factors, knowledge and risk perception of cervical cancer	China	Cross-sectional survey	167 women (142 who intended to receive future screening, 25 who did not)	KQ1–2
Hoque et al. ³⁹	Evaluation of cervical cancer screening program at a rural community of South Africa	South Africa	Cross-sectional survey	611 women older than 30 years	KQ1–2

(continued)

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up (continued)

Author and reference	Study title	Country	Study design	Study population	Key question
Keshavarz et al. ⁴⁰	Factors for performing breast and cervix cancer screening by Iranian female workers: a qualitative-model study	Iran	FG, IDI	70 female factory workers aged 20–45	KQ1–2
Kim et al. ⁴¹	Influencing women's actions on cervical cancer screening and treatment in Karawang District, Indonesia	Indonesia	FG, IDI	20 husbands, 20 women, 4 doctors, 8 midwives (all female), 16 members from community advocacy team, 3 district health officials	KQ1–4
Lyimo et al. ⁴²	Demographic, knowledge, attitudinal, and accessibility factors associated with uptake of cervical cancer screening among women in a rural district of Tanzania: three public policy implications	Tanzania	FGs IDI	354 women aged 18–69 living in Moshi Rural District	KQ1–2
Moreira et al. ⁴³	Knowledge and attitudes about human papillomavirus, Pap smears, and cervical cancer among young women in Brazil: implications for health education and prevention	Brazil	Cross-sectional survey	204 women aged 16–24	KQ2

(continued)

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up (continued)

Author and reference	Study title	Country	Study design	Study population	Key question
Mosavel et al. ⁴⁴	Cervical cancer attitudes and beliefs— a Cape Town community responds on World Cancer Day	South Africa	Cross-sectional survey	228 women drawn from two events on World Cancer Day	KQ2
Mupepi et al. ⁴⁵	Knowledge, attitudes, and demographic factors influencing cervical cancer screening behavior of Zimbabwean women	Zimbabwe	Cross-sectional survey	514 women aged 12–84	KQ1–2
Ndikom et al. ⁴⁶	Awareness, perception and factors affecting utilization of cervical cancer screening services among women in Ibadan, Nigeria: a qualitative study	Nigeria	FG	82 female participants aged 16–40 recruited from antenatal clinics	KQ1–2
Nene et al. ⁴⁷	Determinants of women's participation in cervical cancer screening trial, Maharashtra, India	India	Randomized controlled trial	100,800 women aged 30–59 invited to screen	KQ1–4
Ngugi et al. ⁴⁸	Factors affecting uptake of cervical cancer early detection measures among women in Thika, Kenya	Kenya	IDI	98 women from the screening and 49 women from the treatment clinic	KQ1–2, 4

(continued)

Characteristics of the literature reviewed on barriers and facilitators to cervical cancer screening and follow-up (continued)

Author and reference	Study title	Country	Study design	Study population	Key question
Stormo et al. ⁴⁹	Bolivian health providers' attitudes toward alternative technologies for cervical cancer prevention: a focus on visual inspection with acetic acid and cryotherapy	Bolivia	Cross-sectional survey	7 nurses and 35 physicians	KQ1–2, 4
Wall et al. ⁵⁰	Modifiable barriers to cervical cancer screening adherence among working women in Mexico	Mexico	Case control	229 female store clerks aged 18–64 (94 nonadherent, 135 adherent)	KQ2
White et al. ⁵¹	“Worse than HIV” or “not as serious as other diseases”? Conceptualization of cervical cancer among newly screened women in Zambia	Zambia	FGs, IDIs	60 women screened at primary health care clinic	KQ1–2, 4
Wong et al. ⁵²	Cervical cancer screening attitudes and beliefs of Malaysian women who have never had a Pap smear: a qualitative study	Malaysia	IDIs	20 non-screened women	KQ1–2, 4

Notes. FG = focus group; IDI = in-depth interview; KQ = key question.

The four key questions (KQs) for our review focused on the facilitators and barriers to cervical cancer screening (KQs 1 and 2) and post-screening follow-up (KQs 3 and 4). We focused on the four levels of actors (i.e., individual, family, community, and health care system).

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Microsimulation Models to Assess Impact of Health Programs to Address Obesity and Low Birth Weight in Indonesia

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Introduction

Noncommunicable diseases (NCDs) accounted for 63 percent of human mortality worldwide in 2008, and the rate is increasing.¹ Given the increasing prevalence of NCDs around the world, countries are designing health programs to prevent onset or treat complications of these diseases to reduce the resulting health and financial burden on their societies. Apart from the challenges to obtain resources to develop these programs (funds, personnel, and capital investments), implementation challenges such as achieving high participation rate and compliance are also a concern. Consequently, the impact of these programs depends on economic and social processes, as well as on the efficacy of the program itself.

Geospatial, dynamic microsimulation is an ideal tool for two purposes in addressing NCDs: (1) to analyze a complex web of interrelated factors and (2) to develop an understanding of what programs or policies might work better than others. As part of a prior study, RTI International staff developed a tool, Forecasting Populations (FPOP),² to assess the impact of population aging on diseases with long latency periods and to link it to the actions and health status of the individual. The context for such analyses involves various characteristics and factors: personal (age, sex, education, and similar factors), social (family and community), economic (family income and community wealth), and location (proximity to program facilities).

Dynamic microsimulation models offer the flexibility to investigate, for example, interrelationships among individuals (e.g., sexual behavior and treatment compliance), causal factors (treatment effectiveness), and disease

traits (secondary infection rates and genetic mutation rates) over time.^{3,4} The models then enable users to examine the influence of changes in demographic and social characteristics as the population's age distribution, composition, and size change as a consequence of the health policy being examined. For example, low birth weight (LBW) is caused by nutrition deficiencies related to poor diet or diarrheal infections. A model of the type described here could assess the relative effectiveness of nutrition supplementation programs versus sanitation improvements.

This study had two main purposes. One was to test the feasibility and utility of microsimulation models for examining the impact (or lack of impact) of clinical or public health interventions over time. These interventions were intended to tackle two difficult NCD-related problems: adult obesity and neonatal LBW. The other purpose of the study was to produce some useful information for health policy makers about interventions that might be worth considering.

Because this project was part of an RTI Grand Challenge concerning low- and middle-income countries (LMICs), we needed data and potential interventions for an LMIC country where both adult obesity and neonatal LBW were prevalent and worrisome and where data were available to populate the assumptions required for the microsimulation models. Because we had recently created a baseline set of population and demographic data for Indonesia, that country became our focus.

The study, which was complex, produced some forecasts of trends in both conditions in Indonesia and investigated the impact of two clinical interventions over time. The investigations limited their outcomes to (1) examining the feasibility of applying microsimulation methods to the NCDs and determining how well the models performed, (2) assessing the type of data that would be needed to develop appropriate model parameters, and (3) determining the type of policy interventions that could be addressed with this model.

The Nutritional Paradox: Obesity and Low Birth Weight

Studies have correlated obesity with many chronic conditions, including type 2 diabetes, cardiovascular diseases, several types of cancer, musculoskeletal disorders, sleep apnea, gallbladder disease, sexual dysfunction, nonalcoholic fatty liver disease, and asthma.⁵⁻⁸ Numerous studies have also found that obese women have a higher risk for pregnancy complications.⁹

For many LMICs, the traditional problems of undernutrition run the risk of being dwarfed by the health problems caused by obesity.¹⁰ In developing countries, obesity has been linked with abundance. This observation suggests that as developing countries improve their economic status and their gross national product, undernutrition should decrease, and obesity should begin to appear among members of the upper socioeconomic classes.¹¹ The relationship between gross national product and overweight is complex, however. Being poor in the poorest countries (those with a per capita gross national product of less than US\$800 per year) appears to “protect against” obesity; however, being poor in a middle-income country is associated with a higher risk of obesity than being richer in the same country is.¹⁰

A manifestation of this nutritional paradox is the common occurrence of underweight children and overweight adults in the same family. This is a new phenomenon in developing countries undergoing the nutrition transition. It is apparently brought about by changes in diet, food availability, and lifestyle that occur in countries experiencing a socioeconomic and demographic transition.

Nutritional processes that occur as part of the human growth and aging process regulate four interrelated conditions: (1) LBW newborns, (2) stunting in neonates, (3) childhood obesity affecting children older than 2 years of age, and (4) adult obesity. Investigating links among these four stages has become a focus of research in the past 20 years. Some researchers have suggested a link between fetal development and obesity later in life. In one study, researchers found that altering the levels of two common hormones, insulin and leptin, in utero changed the cellular development in the region of the brain that regulates appetite.¹² Hence, altered levels of leptin and insulin may have marked effects on brain development in offspring; this finding provides further clues to the causes of obesity.¹² LBW has been associated with several chronic diseases in adults, including hypertension, diabetes mellitus, and obesity.¹³

The Current Situation in Indonesia

These results emphasize the need to prevent growth retardation by promoting prenatal care and breastfeeding and controlling infectious diseases. Consequently, we developed a model that portrays the burden of undernutrition and its potential influence on the epidemiology of obesity. We chose Indonesia as the country of focus for several reasons: we had previously developed a simulated baseline population for Indonesia, which could be used to populate our model; Indonesia has significant LBW and obesity issues; there is a unique longitudinal data source for Indonesia;¹⁴ and we have

several in-country collaborators. In addition, Indonesia is in the process of establishing a comprehensive national public health policy. A model like the one presented here could help health planners design specific policy features for future health care requirements.

Obesity: Epidemiology

Obesity is a serious problem in Indonesia. The current estimate is that 67 percent of Jakartans are overweight or obese.¹⁵ Across the entire country, obesity has increased in all population groups, including rural and low-income strata, over the past 20 years.¹⁵ Using cutoff values appropriate for an Asian population¹⁶ to define obesity, the proportion of the population that is obese increased from about 8 percent in 1993 to 17 percent in 2007. (The percentages differ depending on the cutoff values used; however, the trend is apparent in all situations.) The portion of the population presenting symptoms of pre-obesity (weight gain, high blood pressure) has increased from 20 percent to 26 percent in the same 14-year period. The 2010 Indonesia Basic Health Research (Riset Kesehatan Dasar, or *RisKesDas*) Study indicates that the problem has continued; in 2010, 22 percent of the population older than 18 years were obese.^{17,18}

Numerous health policy alternatives have been proposed to address obesity. These include the following approaches:

- changing behaviors (e.g., nutrition awareness and food choices, exercise participation)
- improving access to ideal nutrition (e.g., availability of nutritional supplements or fresh fruit and vegetables)
- improving treatment availability and quality (e.g., establishing more local clinics in addition to tertiary health centers)
- implementing monetary incentives (e.g., tax on certain foods, tax incentives to lose weight, or subsidized selected foods).

Key strategies focus specifically on nutrition and food choice education, treatment availability, nutritional supplements, food subsidies, food taxes, and exercise programs and facilities.

Low Birth Weight: Epidemiology

Maternal nutritional deficiencies at conception and during pregnancy are associated with an increased risk of LBW and childhood stunting.¹⁹ Globally,

approximately 16 percent of all live births, or nearly 22 million newborns, weigh less than 2,500 grams (the definition of LBW). LBW is the single most important factor influencing neonatal mortality and is a significant determinant of infant morbidity and mortality.

Because maternal undernutrition is a major determinant of LBW in developing countries, high rates of LBW should be interpreted not merely as indicators of undernutrition, morbidity, and mortality for the newborn but also as an urgent public health warning that women of childbearing age are undernourished.^{20,21} Furthermore, research demonstrates that after 2 years of age, stunting brought on by LBW occurrences is difficult to reverse. Also, over the life cycle, these children have a greater likelihood of becoming obese and developing chronic disease as adults.²² Unless these trends are studied and appropriate public health responses are employed, a health disaster of diet-related NCDs will unfold, with the poorest patients suffering the most because they will not be able to afford treatment.²³

Microsimulation Models to Evaluate LBW and Obesity Trends

As a first step, our focus was on developing a model for each condition with the goal of connecting LBW and adult obesity in a comprehensive model in the near future. In its current form, our study demonstrated the following:

- Microsimulation models of LBW and obesity can be useful tools in the hands of appropriate policy makers.
- Studies can measure regional and national impacts of clinically specific interventions.
- Patients will participate in nutrient-based intervention programs if they have access to clinics that support the intervention.
- Static clinical data sources limit the type of investigations that can be accomplished by a simulation model. The Indonesia Family Life Survey (IFLS)¹⁴ is a longitudinal data set that can be used to measure changes in patients' characteristics and their environment as they age. Hence, IFLS can be useful in investigating the ramifications of LBW and the connections between LBW and adult obesity.

The effectiveness of health policy interventions depends both on whether the Indonesian health care system provides diagnostic, preventive, and treatment services and on individual patients' willingness to use those services and participate in health programs. To assess participation rates, we

collaborated with researchers at SurveyMETER (<http://www.surveymeter.org>) to design and implement a survey to measure mothers' willingness to participate in a nutrition supplement program. This survey is described in the Methods section under "Preference Survey to Estimate Participation Rates for the Low Birth Weight Model."

Table 3.1 presents the primary questions we sought to address in this study.

Table 3.1 Study issues addressed by the Indonesia models

- How prevalent will obesity and low birth weight (LBW) be in the next 50 years in Indonesia?

- What possible unintended consequences (such as high clinic utilization) will obesity or LBW cause?

- How effective will the interventions be for reducing obesity and LBW profiles?

- How effective will the interventions be for reducing obesity- and LBW-related conditions?

Methods

The Microsimulation Models

For this project, we took an existing microsimulation framework tool called FPOP (Forecasting Populations)² that we developed before this study and linked it to Indonesian population "synthetic" data.²⁴ We then added program logic to represent two separate conditions—LBW and adult obesity—to simulate the population aging process, while simultaneously tracking changes in obesity and LBW patterns. Although we developed the baseline data for all of Indonesia, we limited our analysis to the provinces of Yogyakarta and Bali. This limited focus permitted a more thorough verification of the changing weight patterns and intervention policies occurring against a backdrop of an aging population.

Forecast Populations Tool Overview

FPOP is a dynamic, discrete-time microsimulation model that incorporates links among life events, changes in household structure, and changes in the attributes of individuals and their location as part of the aging process. Individuals can be tracked over the life course for decades.² The life events that modify households and populations include birth, marriage/union formation and dissolution, migration, aging, and death. The model determines

the occurrence of life events at each discrete time step stochastically, using empirically derived transition probabilities.

We calculated the initial transition probability parameters for FPOP using Indonesian national census data and health information data. The FPOP model linked to an existing, spatially explicit synthetic baseline population that represented the Indonesian household population in 2010. The baseline population provided the households and persons for whom FPOP simulated and projected life events.

One major advantage of microsimulation models is their ability to examine the effects of alternative scenarios over time. Such scenarios are useful for understanding the sensitivity of key outcomes to demographic or policy changes. For example, one can use microsimulation methods to examine the future population distribution under different demographic or social scenarios or to estimate the long-term performance of various programs or policies.

FPOP's life event probability tables are easily modifiable either to test existing policy scenarios and existing demographic trends or to test hypothetical policy and demographic scenarios. These life event probabilities are common to all birth-death population scenarios. We added LBW and obesity attributes to the simulated population so that we could assess how patterns external to FPOP would affect the population projections.

In general, the availability of appropriate data limits this type of approach. Accordingly, we used several approaches to obtain data to set the parameters for our model. Sources included RTI's Indonesia synthetic population, Indonesian census data, and IFLS data.^{14,24,25} One key model parameter was intervention participation. Specifically, we needed to be able to predict the proportion of females who would participate in the LBW intervention. Accordingly, we developed and fielded a preference survey (with SurveyMETER) that targeted women of birth age to simulate a micronutrient supplementation intervention. This intervention reported a 16 percent reduction in LBW, as described by Bhutta et al.²⁶ The results of the survey were used to identify which women would participate in the intervention.

The microsimulation discussed in this chapter was based on an initial synthetic population in which each individual is described by several characteristics. These include, but are not limited to, sex, age, race, ethnicity, education, and family type.

Table 3.2 lists the various characteristics required, the source of the data, and the geographic level of detail for the simulated data set. The product of these data is an initial synthetic population of Indonesia that represents each of the 61.4 million households and 237.6 million people in that country.

Table 3.2 Demographic characteristics applied as parameters to the Indonesian synthetic population

Characteristic	Source of estimate	Geospatial level of estimate
Demographics of synthetic population	IPUMS 2010 ²⁷	Regency (i.e., a political subdivision of a province)
Household location	LandScan 2012 ²⁸	1 kilometer cell unit
Height	IFLS2007 ¹⁴	Province
Weight	IFLS2007 ¹⁴	Province

Sources: International Public Use Microdata Series (IPUMS 2010)²⁷; LandScan²⁸; Indonesia Family Life Survey 2007 (IFLS2007).¹⁴

Obesity Model Overview

A major assumption behind the obesity model application is that the body mass index (BMI) measure indicates adult nutritional status. (BMI is a person's weight in kilograms divided by his or her height in meters squared.) The US National Institutes of Health (NIH) now defines normal weight, overweight, and obesity according to BMI. A second assumption is that changes in BMI reflect changes in overall levels of obesity. Thus, predictions of future numbers of people with high BMIs are used to assess the effectiveness of obesity prevention programs and, accordingly, provide the effectiveness component of a cost-effectiveness analysis. In addition, the predictions will indicate to both policy makers and the community at large the potential scale of the obesity epidemic and whether hypothetical interventions are likely to be effective in limiting the epidemic.

The first step in the process was to assign the baseline height and weight for adults by age and sex from the 2007 IFLS (hereafter "IFLS2007") to the baseline synthetic population.¹⁴ Because the Indonesian synthetic population does not contain BMI, height, and weight as characteristics assigned to each person, we used the IFLS2007 survey, which does contain measures of BMI, height, and weight for each survey respondent.

We summarized these key variables by age, sex, and urban or rural location to determine the mean, maximum, minimum, and standard deviation values by demographic covariate. Also, we summarized the distribution of weight

in each BMI range (using the WHO eight-category BMI standard definitions shown in Table 3.3). Then we assigned weight to each synthetic person based on the distributions by age, sex, and urban/rural location. Next, based on the assigned weight for each individual, we estimated and assigned a BMI value to each individual. Having assigned a BMI and weight value for each individual, we then solved for height and assigned a height to each synthetic person.

Table 3.3 The international classification of adult underweight, overweight, and obesity according to BMI

Octile	Classification	Body mass index (BMI) (kg/m ²) range
1	Severe thinness	< 16.00
2	Moderate thinness	16.00–16.99
3	Mild thinness	17.00–18.49
4	Normal	18.50–24.99
5	Pre-obese	25.00–29.99
6	Obese class I	30.00–34.99
7	Obese class II	35.00–39.99
8	Obese class III	More than 40

Source: World Health Organization, 2016.¹⁶

The simulation phase assigned adult persons an annual weight change in kilograms. The model assumed height to be constant for each individual man or woman for the duration of the simulation. The subject's age, sex, and BMI determine which weight distribution to use in this calculation. In this case, we used the weight trajectories for this calculation derived from US data.²⁹ We took the baseline weight value for men and women and simulated an annual weight change every year. Every year, each individual's weight change was sampled from a normal distribution with a mean annual weight change and standard deviation estimated from IFLS2007 by sex and urban/rural location. The yearly percentage changes were assumed to be between -0.5 BMI units and 2.0 BMI units and no greater than 10 percent of the current weight. The minimum BMI was set to 16.

Finally, we introduced a behavioral intervention to reduce the level of obesity in the adult Indonesian population. A literature search revealed that scant evidence exists for obesity interventions within Indonesia. Because of this lack of evidence, our intervention assumed the structure of a general

behavioral treatment based on an example reported by LeBlanc and colleagues that targeted behavioral interventions involving overweight or obese US adults.³⁰ The advantage of this assumption is that the authors examined a broad array of interventions, ranging from physical activity to cognitive therapy.³⁰ The resulting effect sizes were moderate: a 3-kilogram loss (2–4 kilograms, 95 percent confidence interval [CI]) between 12 and 18 months. We simulated their reported effect size for 1 year.

To implement an intervention, a subset of the “simulated” persons participate and as a consequence reduce their BMI by 3 kilograms (2–4, 95 percent CI) for 12 months during the intervention phase. After the intervention and maintenance period, the pre-intervention weight trajectory resumes. Over time, changes to nutritional state occur as changes to BMI occur. When BMI levels dictate, persons move into new nutritional categories. As time advances, subjects move to new BMI categories according to the change in their BMI projections. Table 3.4 summarizes parameter estimates and statistical model assumptions used in the obesity model.

Table 3.4 Parameters and sources of estimates for the obesity model

Parameter	Source of parameter estimate	Statistical model assumption	Explanatory variables
Baseline height and weight	Indonesia Family Life Survey ¹⁴	Sample from normal distribution based on explanatory variables	Age, sex, urban/rural status
Weight trajectories	National Longitudinal Survey of Youth ²⁹	Annual mean change	Sex and BMI category
Intervention efficacy	Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? ²⁶	Annual mean change	Initial BMI category

BMI = body mass index.

Sources: Indonesia Family Life Survey 2007 (IFLS2007)¹⁴; National Longitudinal Survey of Youth (NLSY79), Table 3²⁹; US Preventive Services Task Force.³⁰

Low Birth Weight Model Overview

The probability of a LBW birth comes from two sources (see Table 3.5). The first source is the Health at a Glance tables compiled by the Organisation for Economic Co-operation and Development (OECD).³¹ A second source

is the Indonesia Demographic and Health Survey (DHS), sponsored by the US Agency for International Development (USAID).³² Although the DHS provides a much lower national figure for LBW, it is also stratified by a number of relevant cofactors including parity, birth order, and urban/rural location. Accordingly, we used the DHS estimate to examine the trends in LBW 50-year profiles without and with the food supplement intervention. We factored into the simulation process the mother's probability of having participated in an intervention during her pregnancy, which is based on the responses to the preference survey. (We report these results in the following section.) Statistically significant variables from the analysis of the survey that influenced the LBW simulation results include distance from the intervention site and age of the mother. If the mother did participate in the intervention, the adjusted probability of an LBW birth replaced the DHS estimate.

Table 3.5 Parameter and source of estimates for low birth weight model

Parameter	Source of parameter estimate	Explanatory variables
National LBW estimate	OECD compilation of indicators from a number of sources including international Health Accounts experts, the World Health Organization, and the World Bank ³¹	Country
Probability of LBW child	USAID Demographic and Health Survey responses ³²	Urban/rural, parity
Participation in intervention	SurveyMETER Survey probit regression	Distance to clinic and age of mother

LBW = low birth weight.

Sources: Organisation for Economic Co-operation and Development (OECD)³¹; US Agency for International Development (USAID).³²

Preference Survey to Estimate Participation Rates for the Low Birth Weight Model

A key variable that is unavailable from any known source is the proportion of women that would participate in a nutrient supplementation intervention. To obtain an estimate of this variable, we conducted a preference survey in collaboration with SurveyMETER, a nongovernmental research institute based in Yogyakarta, Indonesia. SurveyMETER staff cooperate with other institutions, policy makers, and researchers both domestically and internationally to design, plan, and implement high-quality data collection. RTI analysts developed the initial survey plan and designed the survey, and

SurveyMETER contributed to the design and carried out all of the field operations.

Initially, the survey presented the respondents with a description of a hypothetical food supplementation program, which was based on programs found to be effective in reducing the risk of LBW deliveries.³³ The survey described the program as lasting 1 year and entailing monthly visits to a specialized health center to receive a month's supply of daily food supplements. As part of the program, health workers would provide advice on preparing healthy meals and would collect anthropometric measurements every 3 months. The program would be provided at no cost.

To model a woman's willingness to participate (i.e., her demand for the program), we created a model based on a standard random utility framework.^{34,35} We measured respondent demand using a single-bounded discrete-choice valuation question (i.e., "Would you [name of participant] agree to participate in this food program?").

Because programs providing daily food supplements are not widely available in Indonesia, we used a contingent valuation method to collect data on intervention participation. This method, which measures respondents' preferences for currently unavailable goods,³⁶ is now widely used in developing countries.^{37,38} The contingent valuation component of our survey asked respondents about their willingness to participate in a hypothetical food supplementation program given a range of possible one-way travel times to the program's health offices. The survey told respondents that they would be required to pay their own travel expenses and they could experience one-way travel times of 10 minutes, 30 minutes, 60 minutes, or 120 minutes. Each travel time was included in the study design. Each respondent was randomly assigned to only one travel time. Our total original sample size of 200 was based on a goal of approximately 50 completed interviews per experimental travel time. (The survey also asked respondents about their willingness to enroll their children younger than the age of 2 years in the same hypothetical food supplementation program, but these data are not analyzed or reported here.)

Sampling Plan and Procedures

The study aimed to conduct 200 household interviews in eight enumeration areas located in two provinces from Java, the most populated island. The provinces were Central Java and Special Region DI Yogyakarta. The sample

was stratified by urban/rural status. The urban enumeration areas were randomly selected from two cities, Semarang (the capital of Central Java) and the city of Yogyakarta (the capital of DI Yogyakarta). The rural enumeration areas in DI Yogyakarta were selected from the other districts in DI Yogyakarta, whereas the rural enumeration areas in Central Java Province were selected from a list of rural villages located in two districts bordering Semarang: Semarang district and Kendal district.

SurveyMETER selected households from lists of households with children younger than 2 and mothers between 18 and 38 years of age acquired from each selected village. Twenty-six households were randomly chosen from each enumeration area's household list. Each selected household was randomly assigned to one of the four questionnaire versions based on one-way travel times. All survey interviews were administered by trained interviewers from SurveyMETER. Completed interviews were electronically submitted to the SurveyMETER office in Yogyakarta, where they were reviewed for data quality; errors were reported to the field team for correction.

The study protocol was reviewed and approved by institutional review boards at RTI and SurveyMETER. In addition, permission to conduct the study was also provided by the Government of Indonesia.

Results

Survey Estimates for Participation Rates

We analyzed the survey data using several probit regression models to determine which variables best explained the respondents' stated willingness to participate in the hypothetical food supplementation program. The findings from this survey indicated that the location of a respondent's residence had a statistically significant effect on stated willingness to participate, but whether the respondent lived in a rural or urban area was not statistically significant. Whether the respondent had moved to a new regency or province in the 5 years prior to the survey did not influence mothers' willingness to participate. Neither did household income, access to better quality drinking water, household size, or ownership of select assets. However, respondents with the following characteristics were less likely to say they would participate: those without a telephone, respondents who owned a motorbike or motorboat, and respondents participating in a state-sponsored poverty alleviation program.

Respondents with a BMI of less than 18.5 (an indication of underweight) were more likely to say they would participate in the hypothetical food supplementation program. However, other variables potentially indicating the respondent's need for supplemental nutrition (i.e., whether or not the respondent was breastfeeding at the time of the survey, had previously given birth to a LBW baby, had participated in a food supplementation program in the past, or had a family history of underweight) did not provide much explanatory power.

Younger women were more likely to say that they would participate in the program. Respondents who were over the age of 19 years were less likely to say they would participate than respondents under the age of 18.

Overall, 74 percent of women reported that they would be willing to participate in the food supplementation program. Willingness to participate declined significantly as the one-way travel time increased ($p < .001$). Although 94 percent of women with an estimated 10-minute one-way travel time and 88 percent with a 30-minute travel time reported that they would participate in the program, the percentage dropped to 67 percent with 60 minutes of travel and to 46 percent with 2 hours of one-way travel.

Probabilities of participation were estimated by travel time to the intervention site and mother's age. Distance, age, size of housing, motorcycle ownership, and presence of a telephone in the house were strong predictors of participation. We set probabilities for mothers older than 38 equal to those for ages 35 to 38 years for the same travel time. All other variates were set to the mean values for the population. Table 3.6 shows the probabilities, which ranged from about 0.1996 to 0.9997. The youngest women (under age 20) were more likely to report that they would participate regardless of travel time. Up to 30 minutes of one-way travel had relatively little effect on women's

Table 3.6 Probability of participation in food supplementation programs by age of woman and travel time to clinic

Age of mother	10 minutes travel	30 minutes travel	60 minutes travel	120 minutes travel
18–19 years	0.9997	0.9986	0.9884	0.7945
20–24 years	0.9855	0.9554	0.8356	0.3190
25–29 years	0.9959	0.9845	0.9243	0.4949
30–34 years	0.9649	0.9078	0.7271	0.1996
35–38 years	0.9856	0.9558	0.8366	0.3204

willingness to participate, regardless of age. An estimated travel time of 120 minutes significantly reduced women's likeliness to participate across all age groups.

Low Birth Weight Model Results

Findings for Incidence of Low Birth Weight Assuming No Intervention

We ran the LBW models for the Yogyakarta and the Bali provinces for 50 years with no intervention (see No Intervention columns for each province in Table 3.7). As expected, the LBW incidence did not change appreciably over the 50-year time period. With no food supplementation intervention, the projected percentage of births that would be LBW births slightly declined for Yogyakarta (7.02 percent to 6.83 percent after 50 years), but the projected percentage of LBW births increased slightly over the same time period for the Bali population (6.92 percent to 7.06 percent).

Table 3.7 Percentage of low birth weight births with and without intervention, by province

Year	Yogyakarta		Bali	
	No Intervention	With Intervention	No Intervention	With Intervention
2010	7.02	6.23	6.92	6.28
2015	6.98	6.37	6.82	6.27
2020	6.77	6.32	6.96	6.12
2025	7.16	6.19	7.14	6.24
2030	6.93	6.17	6.77	6.20
2035	6.85	6.19	6.96	6.06
2040	7.02	6.20	9.95	6.29
2045	6.87	6.17	6.96	6.06
2050	7.00	6.35	6.97	6.23
2055	6.83	6.21	7.06	6.03

Note that the baseline fertility rates were lower in Yogyakarta (1.94 births per 1,000 women aged 15–44 in a calendar year) than in Bali (2.13 births per 1,000 women).³⁹ Consequently, estimated population growth in Bali grew by 30 to 40 percent over the projected time period. By contrast, in Yogyakarta,

overall population growth was 14 percent over the same time period. These findings indicate that unless immigration is significant, by 2055, Yogyakarta will have an older population.

Findings for Incidence of Low Birth Weight Assuming an Intervention and Variable Participation Rates

When we introduced into the model the participation rates shown in Table 3-6, the reduction in LBW incidence was modest (see Table 3-7). In Yogyakarta, LBW incidence went down 11.3 percent in the first year (from 7.02 percent to 6.23 percent). This reduction dropped to 9 percent (from 6.83 percent to 6.21 percent) in 2055. In Bali, the decrease in LBW incidence was 9.2 percent in year 2010 and increased to 14.6 percent in year 2055. Note that participation rates were slightly lower in Bali reflecting the slightly longer travel times in Bali relative to Yogyakarta to the clinics that administered the intervention.

Obesity Model Results

Unlike the LBW model, no participation rate estimates were available for the obesity model, and we did not develop a survey to obtain an estimate of obesity intervention participation. Consequently, we simulated participation rates of 0, 25, 50, 75, and 100 percent, all beginning from the baseline year (2010) estimate. The results can be viewed as a sensitivity analysis of the participation rate estimates.

The WHO defines eight weight categories based on the BMI classifications shown in Table 3-3 earlier in the chapter. We stratified our population into these eight BMI categories (three classifications of thinness; normal; pre-obese; and three classifications of obesity).

We assumed that participation in the behavioral intervention yielded a modest mean weight loss of 3 kilograms distributed over a 1-year period plus a 1-year maintenance period. All year-long intervention or maintenance periods started at the baseline year (2010). We assumed further that individuals resumed their previous annual weight trajectory after completing the intervention period. The participants in the intervention were the pre-obese and obese individuals identified in the model as persons with a BMI greater than 27.5.

Table 3.8 shows the baseline BMI distribution (percentage of total) in Yogyakarta, by age group and BMI classification.

When we ran the model for 30 years without the intervention (see Table 3.9), the projected obesity rates increased substantially over the 30-

Table 3.8 Distribution of adults in Yogyakarta across obesity classifications, by age group: year 0

BMI Classification	Age Groups				
	25–34	35–44	45–54	55–64	65–100
Severe thinness	2.12%	0.92%	1.55%	2.89%	4.98%
Moderate thinness	2.95%	1.76%	2.21%	3.12%	5.60%
Mild thinness	7.72%	5.53%	5.94%	7.7%	13.57%
Normal	59.66%	53.76%	54.00%	55.96%	61.31%
Pre-obese	23.69%	30.37%	28.67%	24.75%	13.12%
Obese class I	3.61%	6.93%	6.95%	5.10%	1.35%
Obese class II	0.24%	0.69%	0.66%	0.46%	0.06%
Obese class III	0.01%	0.04%	0.02%	0.02%	0.01%
Total	100.00%	100.00%	100.00%	100.00%	100.00%

Table 3.9 Distribution of adults in Yogyakarta across obesity classifications, by age group: year 30, with no intervention

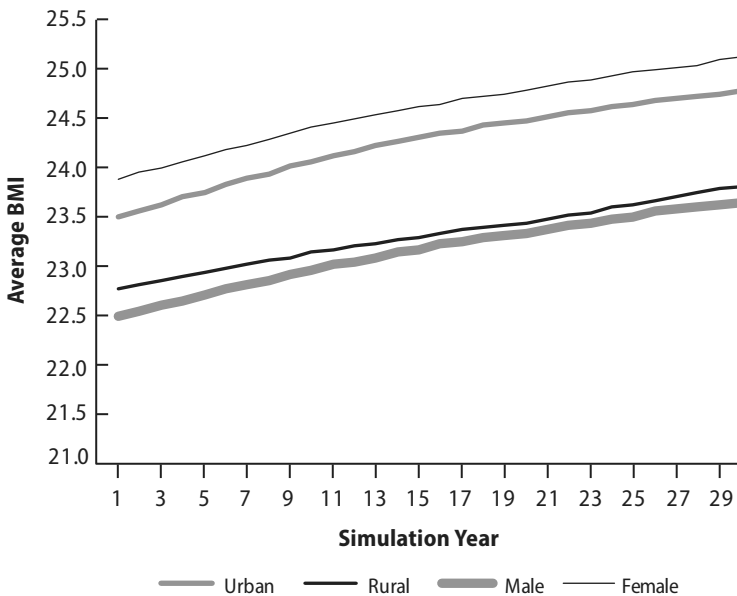
BMI Classification	Age Groups				
	25–34	35–44	45–54	55–64	65–100
Severe thinness	0.41%	0.20%	0.35%	0.57%	0.65%
Moderate thinness	5.56%	3.51%	4.27%	6.24%	11.70%
Mild thinness	7.40%	5.33%	5.72%	7.29%	11.92%
Normal	56.74%	50.94%	50.02%	52.09%	46.00%
Pre-obese	24.91%	30.56%	29.80%	25.85%	17.18%
Obese class I	4.58%	8.33%	9.10%	6.96%	6.02%
Obese class II	0.38%	1.05%	0.66%	0.95%	2.72%
Obese class III	0.02%	0.08%	0.08%	0.05%	3.81%
Obese class III	0.01%	0.04%	0.02%	0.02%	0.01%
Total	100.00%	100.00%	100.00%	100.00%	100.00%

year period. For example, the frequency of obese individuals (categories 6–8) ages 45 to 54 years rose from 7.63 percent ($6.95 + 0.66 + 0.02$) to 9.84 percent. In the oldest group (ages 65 or older), the increase of overweight and obese subjects (categories 5–8) more than doubled, from 14.55 to 29.73 percent. In contrast, at the start of the simulation, almost 60 percent of the women in the youngest age group had normal BMI; after 30 years, with no intervention, this number was reduced to 57 percent.

We also ran simulations with varying rates of participation to compare the effects of increasing participation rates in the intervention. Simulations like this can demonstrate to decision makers what target participation rate would be needed to offset the natural rise in BMI rates that would occur naturally (as Tables 3.8 and 3.9 reflect).

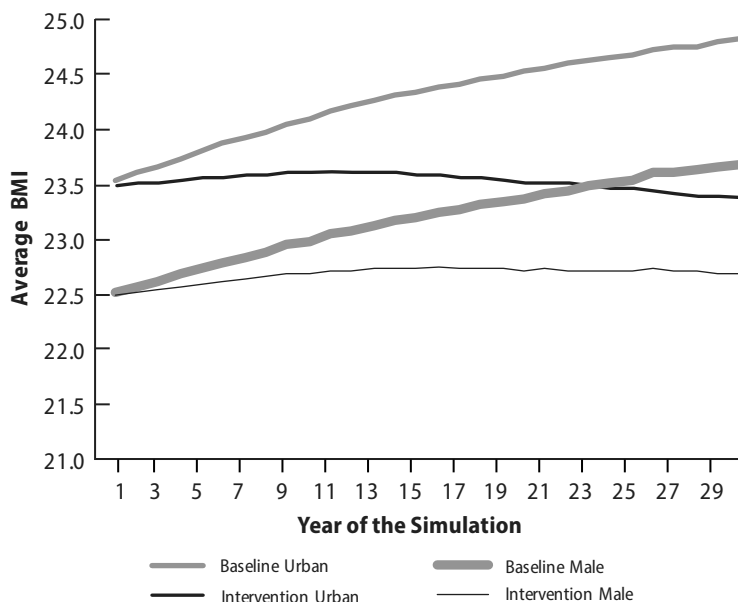
We combined the population of adults older than 24 years of age from the two provinces and then separated that group by male vs. female and by urban vs. rural location. Figure 3.1 presents the average BMI of the groups over a 30-year period in the absence of an intervention.

Figure 3.1 Average adult BMI over 30 years, by year, urbanicity, and sex: no intervention



The growth curve of average BMI for females approximates the curve for males; the same growth pattern holds for rural and urban adults. Figure 3.2 compares the average BMI profiles of males and of urban adults over 30 years under no intervention from Figure 3.1 (baseline) with the profiles of those groups after 30 years if 25 percent of the adult population participated in the intervention. For simplicity of presentation, we dropped rural adults and females from Figure 3.2, since both groups respond to the intervention

Figure 3.2 Average urban and male adult BMI over 30 years, by year: baseline (no intervention) versus 25 percent participation in the intervention



in a manner consistent with urban adults and males. Over the 30-year simulation period, an intervention involving 25 percent of the participation approximately flattens out the growth curve of average BMI for all groups examined compared with preintervention levels. In other words, a 25 percent participation would maintain the status quo.

Discussion

Our Modeling Approach

A major goal of our study was to demonstrate that by wedding an external disease or condition to the FPOP framework, we could produce a robust model capable of performing intervention assessments. We demonstrated this capability for two conditions: LBW and obesity. As documented earlier, these conditions are problematic in Indonesia specifically and in LMICs generally. LBW births and obesity are both major risk factors for numerous chronic diseases, including diabetes, cardiovascular diseases, and cancer. Thus, they both appeared to be appropriate choices, and we decided to implement both.

Eventually, we realized that the two conditions were related in the sense that it is common for survivors of LBW to become obese as adults. The linkage between the two conditions is a third condition—namely, stunting (below -2 standard deviations from median height for age of the reference population). This condition can occur at birth or can develop during preadolescence, but examining it was beyond the scope of this pilot project for the RTI Grand Challenge. Consequently, we developed the two models but did not attempt to connect them.

Our modeling approach was a natural mechanism for testing hypotheses regarding LBW and obesity projections. In addition, we provided examples that demonstrated how users of FPOP could integrate interventions into the models.

Apart from the epidemiology and risks of these disorders in Indonesia, we selected Indonesia because of two other factors: RTI International maintains a formal regional office in Jakarta, Indonesia, and we had good contacts within the country. One of these contacts was SurveyMETER, whose staff became part of the study team and with whom we developed a collegial partnership.

Impact of Interventions

The specific impacts we simulated in the two FPOP models were straightforward exercises. In the case of the LBW model, our results demonstrated that the effectiveness of an intervention depends on the initial birthrate and the regional and demographic factors that influence LBW occurrences. The specific intervention was based on a highly regarded clinical study that had been designed to limit the occurrence of LBW. This particular example demonstrated one of the features of a FPOP-type model; namely, to take the results of a clinical trial and extend the trial results to a target population. In the case presented here, LBW births, as reported in the DHS survey,³² are sufficiently low that the intervention demonstrated little impact.

The obesity model demonstrated that if the status quo prevails in Indonesia (i.e., that the weight gain patterns continue as they have since 2007), the obesity profiles in Indonesia reflect disturbing trends. Large future weight gains are predicted for both men and women living in both urban and rural areas. Offsetting these baseline weight gains would require a national campaign involving exercise and food choices, and such a campaign would need to be sustained over a 30-year time period.

Application of the Microsimulation Models

All computer models are simplifications of reality. They can never account for every possible factor or interaction. For that reason, our current results likely underestimated the consequences of the obesity epidemic and the LBW problem. However, our obesity model demonstrated that continuing high rates of obesity among the working-age population may adversely affect national productivity and contribute to negative health consequences for a rapidly growing Indonesian population.

What our exercise produced is a model that in the right hands can be a valuable planning tool for managing a worrisome problem that is becoming more prevalent in developing countries generally. This model can be applied to any country that has comprehensive data with which to generate both the baseline synthetic population and the parameter estimates for the disease models.

Our version of the model addressed obesity and LBW. However, the model can incorporate any addressable noncommunicable disorder and, if appropriate, definable prevention and treatment programs.

The Future

No single model currently exists that accommodates the individual (e.g., nutrition), household (e.g., parent education), and community (e.g., sanitation) risk factors that determine physical growth and development throughout the life stages of Indonesians or any other LMIC. The rapid technical, environmental, and economic changes taking place across the landscape of developing countries are dramatic and will have major future health consequences.

Various clinical and epidemiological studies examine associations between single risk factors (e.g., maternal nutrition) and stunting or obesity. No model yet exists for evaluating simultaneously how the complex interplay between individuals and the environment affects stunting and obesity risk. Our model is the beginning of that development.

Applying our model can pave the way for improving the health of children and adults of future generations by connecting the two models to target the double burden of malnutrition as a whole. Poor infant nutrition is a major risk factor for chronic diseases, in particular abdominal obesity, type 2 diabetes, hypertension, and cardiovascular disease.⁴⁰ The model can identify policies for preventing LBW, stunting, and obesity across the diverse Indonesian

landscape. It can also identify region-specific approaches, a necessity for a country with limited resources and a decentralized health care system.

Conclusions

Our main accomplishments include the following:

- We developed two separate NCD models that we applied to Indonesia: adult obesity and LBW births.
- We linked each model to a spatially explicit, synthetic baseline population of Indonesians generated from a microdata sample of the Indonesian 2010 census.
- To facilitate model development, we used an existing modeling framework that can be adapted to most NCD scenarios.
- We used the IFLS panel survey, census data, health surveys, and a small in-house survey to develop model parameters.
- We applied and demonstrated a separate intervention to each disease. By simulating and collecting outcome measures with and without the intervention, we interpreted the potential benefit of the intervention.

This experience galvanized our interest, and we are currently seeking processes to broaden model development.

Key Findings and Lessons Learned

- The Forecast Populations (FPOP) tool greatly facilitated model development.
- All simulation models need a baseline population to process. The synthetic data approach supports this process with efficiency and accuracy.
- FPOP and synthetic data available are insufficient for modeling noncommunicable diseases (NCDs) without additional clinical data that describe disease-linked measurements and changes in those measurements because of aging. The specific conditions depend on the NCD.
- The two NCDs we modeled are biologically connected in the sense that being a low-birth-weight infant increases the risk of adult obesity.
- The linkage between the two conditions is stunting. A stunted child reflects severe sustained malnutrition, which is difficult—and perhaps impossible—to overcome.

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Supporting Diabetes Medication Understanding and Adherence Through a Health Literacy Intervention, Medication, in Kerala, India

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Introduction

People with diabetes need to reach and maintain health targets for glycemic, blood pressure, and lipid control; make sustained behavioral changes (healthy diet, activity, and habits—including smoking cessation and medication adherence);¹ and follow recommended care plans over time. Only with these steps can patients avoid serious diabetes complications, medication side effects, and increased use of health resources. This is true for both developed and low- to middle-income (LMIC) countries.²

The explosive growth in the prevalence of diabetes in India has intensified the public health challenge of helping patients have and follow an appropriate diabetes care plan. Visit-based care for patients is an important opportunity for patient and family interactions with a physician. However, many challenges accompany visit-based care. Communication between patients and their care team is not always effective.³ Supporting patients in managing their own diabetes requires additional visit time and skills, which are often under-resourced.⁴ Individuals must use visits and other resources to develop sufficient diabetes knowledge, coordinate interactions with different members of the clinical team, and sustain their efforts and motivation over time to avoid diabetes-related harm.⁵ The Chronic Care Model developed in 1998 by Dr. Edward Wagner and his team⁶⁻⁸ highlights important activities, people, and systems that interact to support quality care in diabetes; it also points to barriers to effective management of care.

Poor adherence to medications contributes to poor outcomes among patients with diabetes and other chronic conditions. Barriers to adherence such as limited patient medication understanding or affordability (or both) can reduce not only adherence, but also medication safety and efficacy.⁹

Health literacy, the “degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions,”¹⁰ affects up to one-half of patients in the United States.¹¹⁻¹³ Limited health literacy can prevent patients from understanding how to avoid a chronic condition in the first place or how to prevent a disease’s complications after its onset, especially in diabetes.¹⁴ Because of its effect on diabetes knowledge, limited health literacy is a contributing factor in medication nonadherence.¹⁵ If patients have limited health literacy, they may decide to stop taking medications unilaterally or use them with the wrong dose or frequency. This problem reduces the intended effects of medicines, and it contributes to troubling drug side effects or drug interactions that may not be brought to the attention of a clinician or pharmacist who can help. Health practitioners often underrecognize limited health literacy,¹² which is not surprising given the limited time they have to counsel patients about medications.¹⁶

The concept of “universal health literacy” has been promoted to advance the notion that, because limited health literacy is widespread, clinicians should approach every patient as if health literacy challenges may be present. Because clear, simple language is helpful to everyone, universal health literacy makes sense.¹⁷ Interventions designed to expand patients’ understanding, to train and support physician communication about medications, and to improve patient self-tracking of medication use can help improve medication adherence and glycemic control.^{1,18,19} These interventions include steps to assess an individual’s skills and knowledge, actions to improve the suitability of educational materials for those with limited health literacy, and ways to educate patients.¹¹ However, interventions to improve health literacy often require time and expertise, both of which are in short supply.

Technology can help considerably to support patient learning about diabetes and serve patients with limited health literacy.^{20,21} Advanced technologies to support diabetes care are increasingly used in the United States and other higher-resource countries in the form of electronic health records, personal health records, sensors (e.g., glucometers, pedometers, home blood pressure cuffs), and decision aids.²² Patient use of web-accessible²³ and mobile tools at work and at home²⁴ offer promising new approaches for fostering patient self-management.

One internet technology, Polyglot Systems’ Meducation (<http://info.meducation.com>), provides drug information to patients in a highly

tailored, readable, understandable format; it serves as a universal health literacy intervention. It supports patients by giving them tailored yet simple medication information designed to maximize understanding through the use of pictograms, large font sizes, simple language, and language translations. For example, patients can see the same tailored information in Malayalam, English, or any of 18 other languages. Meducation supports providers by supplying state-of-the-art information to patients beyond what the providers typically have time or training to provide.

To investigate the feasibility of using this tailored health literacy intervention in an outpatient diabetes clinic, we designed a feasibility pilot to install and use Meducation at the Medical Trust Hospital (MTH) and Diabetes Care Centre in Kulanada, Kerala, India. The specific aim of this pilot project was to learn what enablers and barriers both patients and staff might experience in this LMIC setting, and to determine what might be needed to scale its use more broadly. A secondary aim was to explore whether using Meducation was associated with any changes in medication knowledge, medication adherence, diabetes learning, patient satisfaction, or glycemic control.

Methods

This was a mixed-methods pilot study of the introduction of Meducation into a diabetes clinic in Kerala, India. We sought to understand the feasibility of this intervention and to understand technology adoption barriers and enablers over a 3-month period. We also collected survey and biometric data to compare the potential impact of the Meducation intervention over time among participants who received it and those who did not.

Approach

The first 6 months of the project (April 1 to September 30, 2013) focused on four key prestudy activities: (1) enhancing and testing the Meducation system (including Malayalam translation of glucose-control medication content); (2) developing and translating study questionnaires, consents, and materials; (3) obtaining institutional review board (IRB) approval at RTI and the Medical Trust Hospital in India; and (4) implementing the Meducation system and training staff. In the next 3 months (October 1, 2013, to February 15, 2014), we recruited participants and collected data. Between February and April 2014, we analyzed and reported results.

Collaborating Teams

This project involved collaborators within RTI and across several organizations. The latter included the St. John's Research Institute in Bangalore, India, the Medical Trust Hospital and Diabetes Care Centre in Kulanada, Kerala, India, and Polyglot Systems, Inc., in Morrisville, North Carolina. Polyglot Systems is a small business that specializes in software tools to address health literacy and health communication challenges.

The MTH is a private hospital with 100 beds and an outpatient center with more than 150 patient visits on a typical day. The hospital is located in the Kulanada district, which is a semi-rural community in the more affluent and well-educated southern state of Kerala, India. The MTH cares primarily for patients with diabetes and its complications. Dr. Vijayakumar and his staff (including several physicians, nurses, nutritionists, and pharmacists) have participated in various grant-funded projects to support community outreach to improve diabetes education, and they are well known for successfully healing the feet of patients with very poor nerve conduction, circulation in the feet, and wound healing.

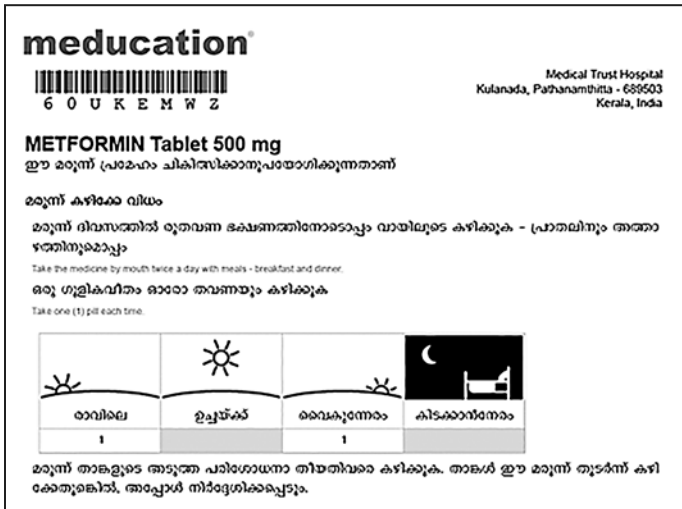
Educational Handouts

Meducation is a commercially available software product that presents tailored medication information in 20 languages (as of March 2016). Materials are written at the fifth- to eighth-grade reading levels, in large fonts. Universal pictographs communicate the medication schedule. It is available in either an online or a printed format. Meducation operates using Software-as-a-Service (SaaS); this requires only a web browser and internet connection, which we provided as part of the study.

For each project participant using a glucose-control medication, we entered prescription information into the system using an anonymous patient identifier, and we provided printouts to the patient. Meducation does not store any patient-identifying information on either a computer or any server. Thus, we had no sensitive data to protect online.

Figure 4.1 illustrates a sample Meducation patient handout presented in the local Malayalam language. The same handout, tailored to the patient, is available in each language that Meducation offers.

Figure 4.1 Meducation handout in Malayalam
















Participants and Group Assignments

Study participants were adults (18 years or older) who spoke Malayalam, had at least one glucose control medication prescribed, were new patients to the MTH, and had monthly follow-up visits scheduled. Recruitment occurred early in the day (around 6 a.m.) as patients arrived for fasting blood work. The study preassigned each clinic day as an “intervention” day or a “nonintervention” day to minimize contamination effects. Consented patients completed questionnaires, had HbA1c (glycolated hemoglobin, a measure of average glucose over a 3-month period) included in their laboratory tests, and received Meducation printouts if they were assigned to the intervention group. We enrolled a total of 130 participants at the start of the study to ensure a minimum of 80 participants at its conclusion. Including the HbA1c measurement also helped to improve patients’ motivation to participate in the study (which paid for the test), because most patients self-pay for laboratory tests and often choose not to obtain the HbA1c even when the clinic physician and clinical staff strongly recommend that they do so.

Measurement

Figure 4.2 shows study activities during patient visits over a 3-month period. All participants completed study questionnaires and received an HbA1c test during their visits at baseline and at 3 months. One-half of the patients received the Meducation handouts; the comparison group did not. We abstracted administrative and clinical data from the medical record at baseline and updated that information after 3 months.

Figure 4.2 Meducation study visits, data collected at each visit, and participants per visit (N = 130): Meducation and comparison groups

	Visit 1	Visit 2	Visit 3
Meducation Group	 Handout  Survey  HbA1c N=65	 Handout  Survey N=47	 Handout  Survey  HbA1c N=41
Comparison Group	 Survey  HbA1c N=65	 Survey N=47	 Survey  HbA1c N=42
	Baseline		3 months

Questionnaire and Qualitative Data. The questionnaire drew items from validated instruments wherever possible and translated them into Malayalam. Table 4.1 describes question content areas, items completed by research staff (sections A, D, and E), and items completed by the patient (sections B and C). Section A collected data about medicine use, section D covered patient demographics, and section E was used to collect medical chart information such as coexisting conditions. Section B included several scales: the 8-item Morisky scale to measure self-reported medication adherence,²⁵ the Treatment Satisfaction Questionnaire for Medication to measure medication use

Table 4.1 Questionnaire content areas

Questionnaire sections	Description
A. Medicine list	Medicines used for diabetes, and other medicines
B. Managing diabetes	
Diabetes Knowledge Test (DKT) plus additional questions ²⁷	Nutritional knowledge regarding carbohydrates, oils, cereals, and dietary habits; HbA1c; exercise; blood sugar testing; care of feet; diabetes complications (DKT) ²⁷
Summary of Diabetes Self-Care Activities ²⁸	Self-care activities practiced during the past 7 days including nutrition, exercise, testing, checking feet, smoking ²⁸
Medication adherence	Morisky Medication Adherence Scale (MMAS-8) plus reasons for missed doses ²⁵
Satisfaction with medicines	Treatment Satisfaction Questionnaire for Medication ²⁶
Social and personal impact of diabetes	Questions from the Diabetes Care Profile about functional limitations due to diabetes; perceptions of efficacy in self-managing diabetes ²⁹
C. Questions about medicine handouts	Questions about the experience using Medication handouts
D. Personal and household characteristics	Demographics; other household information such as years of education, marital status, worked in the past 7 days
E. Patient chart information	Patient height, weight, last HbA1c, prescribed medicines, medical conditions

experience,²⁶ the Michigan Diabetes Knowledge Test to measure patient understanding,²⁷ and the Summary of Diabetes Self-Care Activities scale to measure self-management activities.²⁸ We developed the Section C items to measure patients' experiences using the Medication handouts.

The research team obtained qualitative information concerning implementation of Medication and its use once during each data collection period through a facilitated staff group discussion. We entered all questionnaire and abstracted chart information into a secure web-based database, Epidata,³⁰ that the MTH uses for research. Data collection and storage was maintained securely and in accordance with IRB-approved protocols at MTH and RTI.

Analysis

We used a mixed-methods approach to analyze the data collected. The primary emphasis was to understand the feasibility of implementing and using the Medication system. In addition, as a secondary analysis, we checked

for the impact of Meducation on patients over time by comparing HbA1c and survey responses at baseline with those obtained at 3 months; we also compared information from the patient group receiving Meducation with information from the comparison group. Specifically, we looked at differences in questionnaire scores for medication adherence, diabetes knowledge, diabetes self-care, and glycemic control (HbA1c) over time. We also examined data from the intervention and the comparison groups to look for differences associated with the use of the Meducation handouts. To compare measures between groups and within groups, we used a *t*-test for continuous data or a chi-squared test for discrete data.

Results

Participants

A total of 130 individuals consented to participate in the study; we assigned 65 to the Meducation group and 65 to the comparison group. As Table 4.2 shows, we saw no statistically significant differences at baseline between groups in sex, age, marital status, employment, or access to the internet. However, fewer Meducation group participants than comparison group patients had health insurance. Participants had an average of 10 years' duration of diabetes;

Table 4.2 Participant baseline characteristics

Characteristics	Comparison group (n = 65)	Meducation group (n = 65)	All (n = 130)
Female (%)	50.8	52.3	51.5
Mean age (years)	53.9	55.0	54.4
Mean time since diagnosis (years)	9.6	9.6	9.6
BMI overall (kg/m ²)	26.0	25.3	25.7
Education (years)	12.2	12.0	12.1
Married (%)	88	94	91
Worked in past 7 days (%)	29	35	32
Has health insurance (%)	40	22*	31
Access to the internet (%)	23	26	25
HbA1c (mg/dl)	10.0	9.6	9.8

BMI = body mass index.

* Difference was significant at $p = .02$.

12 years of education; a body mass index of 25.7 (normal is less than 25); and an HbA1c of 9.8 (normal is less than 7.0).

Changes Over Time in the Meducation Group

We compared measurements obtained at baseline and those obtained after 3 months for the participants in the Meducation group.

Diabetes Awareness, Knowledge, and Behavior

Table 4.3 shows the average values among participants using Meducation for numerous measures taken at baseline and after 3 months. Each area improved except for one measure—overall satisfaction with diabetes medications—which grew worse. Although 83 percent of participants perceived diabetes self-care to be important at baseline, they scored, on average, 7.6 out of 13 possible points on the Diabetes Knowledge Test and reported engaging in daily self-

Table 4.3 Changes over time in diabetes survey items and HbA1c for Meducation participants seen at baseline and 3 months later (up to 42 participants)

Survey items and laboratory test	Mean at baseline	Mean at 3 months	Change	Significance
Diabetes self-care (% somewhat or extremely important)	83	96	Improved	p < .001 (n = 42)
Diabetes Knowledge Test (score out of 13)	7.6	10.2	Improved	p < .001 (n = 42)
Summary of Diabetes Self-Care Activities score (7 days)	2.9	3.4	Improved	p < .001 (n = 42)
Satisfaction with diabetes medicines (% very dissatisfied)	28	69	Worsened	p < .001 (n = 36)
Side effects for diabetes medications (% yes)	34	6	Improved	p < .001 (n = 35)
Reported missed medication doses in the last week (%)	29	29	No change	ns (n = 38)
Morisky Medication Adherence (MMAS-8; high or medium, %)	39	53	Improved	p < .23 (n = 38)
HbA1c (mg/dl) (laboratory test)	9.6	8.3	Improved	p < .01 (n = 42)

ns = not significant.

management behaviors 2.9 days per week (41 percent of 7 days) at baseline, which rose to 3.4 days per week (48 percent) at 3 months.

Diabetes Medicines Over Time

Participants in the Meducation group reported dissatisfaction with their diabetes medicines (Table 4.3). At baseline, 28 percent were “very dissatisfied,” and this value had worsened significantly at 3 months. Other measures improved significantly (side effects) or did not change (missing a medication dose in the previous week) over time. Using the 8-item Morisky Medication Adherence Scale (MMAS-8), 39 percent showed high or medium adherence; the remainder (61 percent) reported low adherence. The MMAS-8 includes general questions about medicine use over a longer time horizon.

HbA1c Testing Over Time

Among Meducation participants (Table 4.3), blood testing for HbA1c showed significant hyperglycemia (9.6 mg/dl) at baseline. These values improved significantly (8.3 mg/dl) at 3 months.

Experience Using the Meducation Tool

Among participants who responded to survey questions about their use of the Meducation tool after 3 months (N ranging from 38 to 41 individuals), more than 90 percent reported easily reading the text, finding it to be informative, being willing to recommend it to a friend, and wanting information for nondiabetes medicines being taken (Table 4.4). Online access issues were endorsed much less frequently, however. Most individuals reported wanting to receive the Meducation information from the physician (60 percent), versus a computer (23 percent) or a pharmacist (13 percent) in the doctor’s office.

Staff Experience

During this study, we conducted informal interviews with MTH staff to learn about their experience using Meducation handouts with patients. They appreciated having the Meducation printouts for the patients and wanted to continue distributing them after the study’s conclusion.

MTH staff found that the process of producing the handouts, which required several steps to select prescribing details for each medicine and print the handout, took 3 to 4 minutes when the internet was functioning well. When the internet was slow, this step took much longer and led to workarounds such as the use of backup electronic documents (PDFs) or

Table 4.4 Participant responses to a survey at 3 months about use of Medication

Survey items and Medication use	N	Results (3 months)
Read the Medication handout	41	98%
Could easily read the text	39	100%
Found it useful, helpful, informative	40	93%
Would recommend to a friend or family member	40	93%
Would like handouts for nondiabetes medicines they take	39	93%
Would be able to access online	40	23%
Would be likely to access online, download, and print	40	15%
Would like to view video for complex medicines*	38	69%
What would you MOST prefer?		
• Printouts from physician	40	60%
• Computer at doctor's office	40	23%
• Printouts from pharmacist	40	13%

* Complex medicine example: metered dose inhaler that requires training.

preprinted documents that provided basic information but were not tailored to the individual patient's medicine dose or schedule. Internet slowing occurred almost every day, although full power outages happened less frequently.

Meducation Group vs. Comparison Group: Survey Results and HbA1c Testing

Overall, survey responses in the Meducation and comparison groups were similar. We did not observe any significant group differences at baseline or at 3 months on several data collection instruments. These included the diabetes knowledge test (DKT); the Summary of Diabetes Self-Care Activities; and the MMAS-8. HbA1c at baseline and at 3 months also did not differ between groups.

Discussion

Major Findings and Implications

Our study of the feasibility of providing medication handouts to patients with diabetes using internet-based technology in an outpatient clinic in India led to several insights and lessons learned. Overall, technical systems worked well.

Patients appreciated receiving the medication handouts. Staff wished to expand use of the system to more patients and to nondiabetes medications such as antihypertensives and others that are commonly prescribed.

Given the enthusiastic patient responses, the design, content, organization, and language (Malayalam) of the Meducation handouts apparently worked well for patients and also pleased the clinic staff. Patients preferred to receive information about medications from their doctor (top choice) or from the pharmacist (second choice), suggesting that the patients did not want only the information. Rather, they wanted the information and an opportunity to discuss it with an expert.

Patients reported a high level of schooling—completion of 12th grade—suggesting high literacy (consistent with regional literacy rates in the State of Kerala). The ability to read is not the same as health literacy, however, and results from study surveys confirmed that knowledge about diabetes showed notable gaps. Patients also reported that they had limited access to the internet, underscoring the value of traditional methods of learning such as patient dialogue with clinicians and staff.

The improvements over time (from visit 1 to visit 3) in patient diabetes knowledge, self-management, medication adherence, and glucose control (as measured by the HbA1c) were encouraging. This progress was not, however, specific to the Meducation handouts or to the participants in the intervention group who received them, and there is still room for further improvement within the intervention.

Our findings suggested that the handouts were not the most important factor influencing diabetes care. Three factors may have contributed to the improvements that we observed over time: (1) patients answered the study questions, which probably served to educate them about diabetes; (2) patients had more time to communicate with staff as they completed their surveys; and (3) patients had increased awareness of their glycemic control via routine testing for HbA1c. The routine care that the MTH provided for patients with diabetes may also have prompted such improvements. Without testing these parameters using comparison groups, however, we cannot draw specific conclusions. With an average disease duration of 10 years, patients seen at the MTH were not new to diabetes. This factor suggests that tailoring diabetes education might be required to serve the needs of individuals who already have knowledge in some areas.

Challenges of the Feasibility Study

We encountered some challenges in this pilot project. First, we had difficulty using the internet to produce the printouts. Although power and internet outages were infrequent (a few per week, on average), internet slowing was very common and made the system unresponsive at times. As a workaround, staff used either preprinted handouts during power loss or prestored PDF copies of handouts during slowing.

Second, staff faced workflow challenges due to the need for additional time with each patient to create handouts and to discuss any questions the patient might have. During the project debrief, staff felt that relocating the production and distribution of the handouts to the pharmacy would be better for patient flow and would permit the patients to spend time with the pharmacist rather than with clinic staff. Staff had also observed that patients spent a large amount of time during the day waiting for appointments with the doctor, the nutritionist, and others. Perhaps this time could be used as an opportunity to offer different or additional types of information and instruction to patients.

Third, surveyed participants reported only modest personal use of the internet. This circumstance may have reflected internet access limitations in the semi-rural community surrounding the MTH; urban internet access was likely higher. Accessing Medication handouts online offers participants with internet access some additional features of this tool, such as different language translations of the same personalized medication instructions. Given that citizens of India speak more than 100 different languages, this feature allows medical personnel, patients, and family members to reduce errors in communication about use of medications.

Fourth, translation from English to Malayalam proceeded smoothly, with small exceptions. One phrase describing the risk of mortality associated with a medication proved to be more difficult than others. The phrase in English suggests a small mortality risk, whereas native speakers found no way to express the risk without saying, in effect, “You will die from this medication.” Research staff eventually decided to strike out the printed text (using a black marker) to avoid misleading the patient.

This illustrates a broader cultural context that may be challenging for research in LMIC countries. The US Food and Drug Administration requires the language about medication risk in the United States, but the agency’s policies are unconnected to the use of medicines in India. More adaptation, including policy work, may be needed if the information about medicines

developed for culturally different countries (e.g., the United States as contrasted with LMIC nations) is used routinely in a different context—here, medical care in India.

Future Research

Our findings suggest several areas for future research. First, greater routine use of HbA1c testing may provide important feedback to patients, caregivers, and clinicians that improves patients' self-management, glycemic control, and motivation. Thus, we suggest that further study is a critical next step to explore the impact of expanded use of the HbA1c on patient engagement.

Moreover, most patients in our study must pay out of pocket for routine laboratory tests, although a growing number of patients have health insurance coverage. The HbA1c in this study was provided at no charge to the participants, so everybody received an HbA1c at each study visit. We wonder, therefore, whether this suggests that health care systems should provide the HbA1c tests free of charge to help their diabetic patients.

Second, community support for patients with diabetes can help patients understand how their behavior contributes to improving (or worsening) their disease. Incorporating better medication information into community education efforts such as KnowDiabetes (<http://knowdiabeteskerala.com/>) could provide tailored medication information for each patient as part of this broader effort. Examining the impact of such interventions would be helpful for clinicians and policy makers alike.

Third, we propose that the critical role of the clinic or retail pharmacist should be examined more thoroughly. The main reason is that patients routinely meet with and speak with their pharmacist to obtain and refill medicine prescriptions and get testing supplies, even more frequently than they interact with the physician, nurse, or diabetes educator. Patients and caregivers tapping into pharmacists' expertise is an important way for them to be able to improve their understanding of medicines. Tools such as Meducation could have a meaningful role in fostering the contributions that pharmacists can make.

Conclusions

The pilot use of internet-based software (namely, Meducation) to produce diabetes medication handouts at the Medical Trust Hospital and Diabetes Care Centre in Kulanada, Kerala, India, demonstrated that the technical systems worked, staff and patients were satisfied with the handouts and would recommend them to others, and clinic staff wished to expand use of the handouts. All participants (with or without handouts) showed improvement over time in their diabetes knowledge, medication adherence, self-care activities, satisfaction with diabetes medications, and measured HbA1c. These improvements may have occurred for several reasons: greater attention and time staff spent with study patients, increased patient learning or focus on self-management behaviors as a byproduct of completing surveys, increased awareness and motivation to achieve glycemic control through HbA1c testing, or other factors.

Cultural factors appear to play an important role in the participation of patients and caregivers in self-management. Growing use of mobile and internet-based tools creates opportunities to leverage technologies in diabetes care. Expanding the use of health information technologies in resource-limited environments such as hospitals, clinics, and community health centers in India holds promise, especially as technology adoption accelerates for both individual patients and the health care industry broadly.

Key Findings and Lessons Learned

- Providing tailored, internet-based patient medication handouts to patients with diabetes in Kerala, India, during their outpatient visit was a feasible intervention.
- Patients and staff were satisfied with the handouts and would recommend them to others.
- Improvements in diabetes knowledge, medication adherence, satisfaction with diabetes medicines, and measured HbA1c were seen in both patients who received the handouts and in those who did not.
- Improvements for those in both the intervention and the comparison groups may be explained by measurement of HbA1c for and research staff giving attention to all patients in the study.
- Clinic staff identified the potential role of the retail pharmacist in using this medication tool with patients, given that pharmacists had a greater number of interactions with patients than physicians, nurses, or other staff had.

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Implementing “Get With The Guidelines” Stroke Program to Improve Health Outcomes of Acute Ischemic Stroke Patients in Shanghai, China

Zhi-Jie Zheng and Kenneth A. LaBresh

Introduction

Ischemic stroke occurs when the blood supply to the brain is interrupted or severely reduced, depriving brain tissue of necessary oxygen and nutrients. Within minutes, brain cells begin to die. Stroke is a leading cause of hospitalization, long-term disability, and mortality in the United States and globally.^{1,2} It is a preventable and treatable disease. Over the past two decades, a growing body of evidence has suggested that more effective primary and secondary prevention strategies, better identification of high-risk individuals, and effective interventions soon after the onset of symptoms are keys to a better patient outcome.³⁻⁶

Patient health outcomes after having an ischemic stroke depend in large part on how and when treatments are administered. Better patient outcomes are often associated with less time between a patient’s arrival to the hospital and administration of treatment. Understanding the care processes that contribute to a better outcome has improved, and now good evidence supports interventions and care processes in stroke rehabilitation.

Get With The Guidelines-Stroke is a US national registry and quality improvement program of the American Heart Association/American Stroke Association; it is part of the larger Get With The Guidelines (GWTG) program. The program supports clinicians’ adherence to evidence-based guidelines in their care of patients hospitalized with stroke.⁷⁻¹⁰ The GWTG-Stroke program is used to improve stroke outcomes in the United States in four ways: (1) generating knowledge through research based on registry data; (2) identifying areas for quality improvement; (3) improving the development of measures, guidelines, and implementation strategies to reduce disparities;

and (4) determining the safety and effectiveness of treatments applied in practice.⁷

More than 40 percent of all patients hospitalized with stroke in the United States are indexed in GWTG-Stroke registry. As of 2013, the registry had recorded more than 2.5 million patient admissions. Studies have demonstrated that all major quality performance measure indicators have improved since the implementation of the GWTG-Stroke programs. These efforts may have contributed to the continuing declines in stroke mortality in the United States.¹¹

Whether GWTG-Stroke can be successful beyond the United States remains to be tested. A key determinant that may hamper broad application of GWTG-Stroke around the world is the diversity of health care systems and economies. Although nations that spend substantially less money on health care than the US may find applying GWTG-Stroke processes difficult, experience in one Brazilian tertiary hospital¹² and in 24 Taiwan hospitals¹³ suggests that GWTG-Stroke could be workable in nations with lower health care expenditures.

In China, which has a population of 1.4 billion, stroke kills approximately 1.6 million individuals each year. This represents an annual stroke mortality rate of 157 per 100,000, exceeding cancer, respiratory disease, and heart disease as the leading cause of mortality and disability in adults.¹⁴⁻¹⁹ The rate of stroke mortality in China is almost 4 times that in developed countries, possibly attributable to the poor acute care management.² In addition, 2.5 million new stroke cases occur each year, and 7.5 million live with some level of disability after surviving a stroke. The geographical difference in stroke incidence in China is marked; the rate is highest in the Northeast (486 per 100,000) and lower in the South (136 per 100,000).

Methods

The objective of this study was to pilot test the feasibility of adapting the GWTG-Stroke program data collection and feedback procedures to the Chinese health care system to facilitate the quality of care improvement effort in one tertiary hospital in Shanghai, China. RTI International provided funding for this pilot project. In addition, we received a small grant (100,000 Chinese Yuan) from the Shanghai Health Bureau to support local staff and data system development. The full GWTG-Stroke program includes a structured quality improvement program based on the model for improvement, which has been implemented in Taiwan and elsewhere. That element of the entire

stroke program was, however, beyond the scope of this specific pilot project in Shanghai.

This pilot study had four specific aims:

1. Develop a Chinese version of an electronic data collection tool and registry system with the goal of integration with electronic health records to support evaluation of care delivery and patient outcomes directly.
2. Deploy a registry data system to collect patient and clinical care information and data.
3. Use stroke care performance measures and individual-level data to evaluate guideline adherence in the hospital.
4. Evaluate the usability and feasibility of such a registry data system for improving the quality of care in Chinese health care system.

Project Site

Our chosen pilot site was 1 of the 12 hospitals affiliated with Shanghai Jiao Tong University School of Medicine. The hospital is considered among the best hospitals in China and has more than 3,200 beds and nearly 5,000 physicians and staff. It provides more than 3 million outpatient visits and 10,000 inpatient services each year. Its neurology department has 54 physicians specializing in various neurological diseases and disorders. The department treats approximately 1,200 stroke patients each year.

Project and Research Staff

Project team members at the selected hospital established a registry team that included specialists and staff in emergency medicine, neurology (stroke), general practitioners, epidemiology, biostatistics, program management and coordination, legal/patient privacy, quality of care assurance, information technology (IT), and database management. One nurse served as the project coordinator; four PhD or MPH students served as research associates or assistants for the project.

The executive team, consisting of the coauthors, neurology department chief, and section chief, assumed responsibility for the administrative, ethical, and scientific decisions that determined the direction of the registry. It made decisions with appropriate input from legal, scientific, and administrative experts. The scientific committee included experts in various areas including

database content, clinical research, and epidemiology and biostatistics. The committee determined the scientific aspects of the registry data system, such as data elements, direction of database inquiries, and specific analyses. It also developed a governance and oversight plan, study policies, a protocol, and an operational manual to guide the process of data collection and quality of care improvement efforts. Institutional Review Board (IRB) approval was obtained from the Shanghai Jiao Tong University School of Medicine.

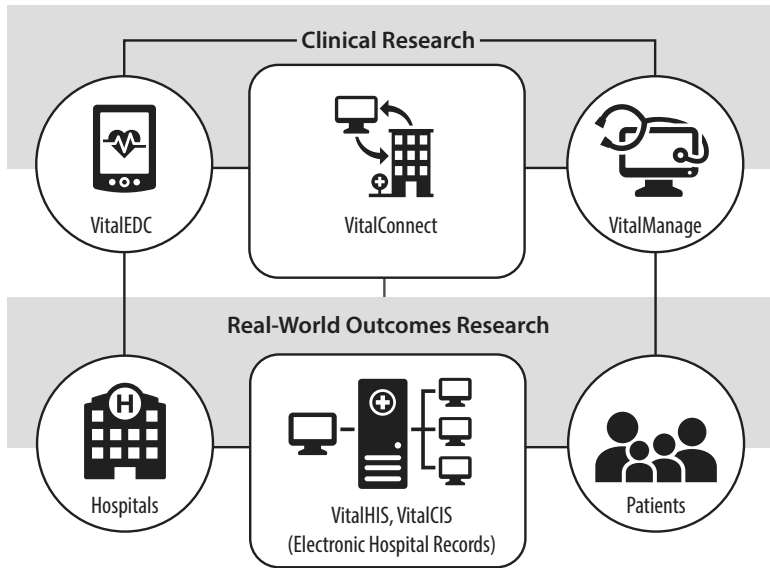
The scientific committee also put the data elements and definitions, patient outcomes, and target population into final form (to fit the specifics of the Chinese health care delivery system). Members also identified patient characteristics, with input from various stakeholders. We developed a unified online data collection interface and registry data system to integrate as much as possible with the hospital's electronic health records and directly support evaluation of care delivery and patient outcomes.

Registry Development

VitalStrategic Research Institute (Shanghai, China) provided subcontractor assistance to develop the data collection tools and system to support the stroke registry. The VitalStrategic Research Platforms have been used in several national registries, including the China Cardiometabolic Registries (CCMR) and the China Chronic Disease Registries (CCDR). The system includes a web-based electronic data capture system, VitalEDC; an electronic hospital records link system, VitalConnect; and a data management system, VitalManage, as well as a health information system (VitalHIS) and clinical information system (VitalCIS) (Figure 5.1).

The stroke registry data elements include the following categories:

- Demographics: age, sex, ethnicity, place of residence, education level, and marriage status
- Prehospital or emergency medical services data: arrival mode, time of arrival, time seen by physician, transfer, in-hospital stroke, direct admit
- Imaging: date and time, initial findings
- Sign and symptom onset: date and time; National Institutes of Health (NIH) Stroke Scale (optional); functional status (optional)
- Thrombolytic therapy: time, complications, reasons for no treatment
- Medical history: stroke or transient ischemic attack, coronary heart disease, peripheral vascular disease, atrial fibrillation, hypertension, smoking, dyslipidemia, diabetes, and obesity

Figure 5.1 Organization of the VitalStrategic stroke registry data system

Source: VitalsStrategic.com. Used with permission.

- In-hospital diagnostic procedures and treatment: atrial fibrillation, time for antithrombotic therapy; deep vein thrombosis prophylaxis; dysphagia screening
- Other in-hospital complications: deep vein thrombosis, pneumonia
- Discharge data: date of discharge, International Classification of Diseases (ICD)–9 codes, discharge destination, functional status, smoking cessation counseling, lipid profile, lipid-lowering medications, antithrombotic medication, and reasons for no treatment, if any.

The following quality measures were used as the indicators for the quality of stroke care:

- Eligible patients who receive acute thrombolytic therapy
- Patients with atrial fibrillation who receive anticoagulation therapy in hospital
- Patients who are evaluated for dysphagia in hospital
- Patients who receive needed antithrombotic, cholesterol lowering, antihypertensive, and diabetes medications at discharge
- Smokers who receive advice and assistance in quitting.

Data Collection

We collected data from consecutive patients before (November to December 2013) and after (March to July 2014) implementation of the new data system. We focused on patients who met one of the predefined case definitions for ischemic stroke, transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhages, and other unspecified types of strokes.

Before implementing the new data system, we used retrospective data collection to obtain baseline data. We identified stroke cases based on ICD-9 codes 430–436 as primary or secondary discharge diagnoses. Trained abstractors conducted chart abstraction based on central or local chart reviews (or both). After implementing the new data system, we used a prospective approach to enroll the cases through active case surveillance (“hot pursuit”) of subjects presenting with stroke-like signs and symptoms to the pilot site hospital. Trained clinical coordinators did all the data collection and abstractions.

Project staff implemented rigorous quality control and assurance processes and a feedback system to ensure the quality of data. Staff were trained to adhere to data collection and coding procedures and protocols. Approximately 10 percent of records were reabstracted to validate the reliability of data.

For this analysis, project staff collected the characteristics of stroke patients and series of quality of care performance indicators before and after implementation of the stroke registry system. We used simple statistics to compare the groups before and after system implementation.

Results

Before implementing the data system, hospital research staff reviewed 445 consecutive cases of stroke over the 2-month period (November and December). Of these, 254 cases (57 percent) were ischemic stroke; 67 (15 percent) transient ischemic attack; 58 (13 percent) intracerebral hemorrhage; 40 (9 percent) subarachnoid hemorrhage; and 39 (6 percent) unknown type. After implementing the new system, we reviewed a total of 878 cases. Of these, 483 (55 percent) were ischemic stroke; 88 (10 percent) transient ischemic attack; 132 (15 percent) intracerebral hemorrhage; 70 (8 percent) subarachnoid hemorrhage; and 105 (12 percent) unknown type.

Table 5.1 shows the characteristics of patients with ischemic stroke before and after the implementation of the electronic system. Patient characteristics

did not differ significantly before and after implementation of the new system. The delay in the time from stroke onset to emergency department arrival in this patient group (i.e., those with ischemic stroke) was considerable. Only 5 to 7 percent of patients arrived in the emergency department within 2 hours of the stroke onset (Table 5.2). The delay time from stroke onset to emergency department arrival did not differ significantly before and after implementation of the new system.

Table 5.1 Characteristics of patients with ischemic stroke before and after registry implementation

Characteristics	Before (N = 254)	After (N = 483)
Men (%)	64	62
Age (years, mean \pm SD)	68 \pm 12	70 \pm 13
Married (%)	60	63
Education less than high school (%)	18	21
High blood pressure (%)	70	72
Total cholesterol over 200 mg/dl (%)	35	38
Ever smoking (%)	56	60
Diabetes (%)	20	24
Atrial fibrillation (%)	12	11

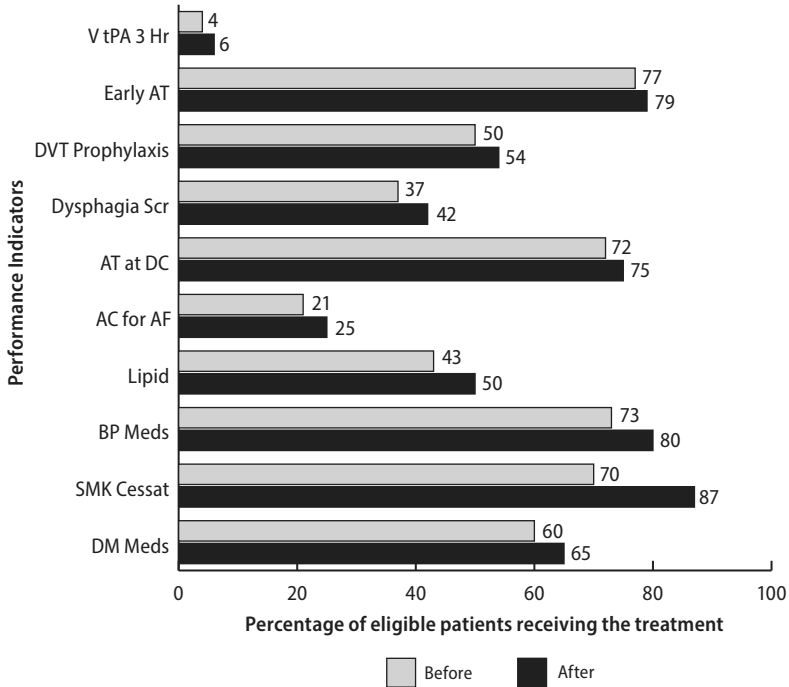
SD = standard deviation.

Table 5.2 Time from ischemic stroke onset to arrival in the emergency department before and after registry implementation

Time Period	Before (%)	After (%)
Less than 2 hours	5	7
2–3 hours	4	5
3–6 hours	10	12
More than 6 hours	32	33
Unknown or missing	49	43

Less than 5 percent of patients received intravenous (IV) tissue plasminogen activator (tPA) in this patient group. However, major quality indicators improved somewhat after the implementation of the new data system (Figure 5.2).

Figure 5.2 Major indicators for stroke care before and after the data collection registry implementation



IV tPA 3 Hr = intravenous tissue plasminogen activator within 3 hours; AT = antithrombotics; DVT = deep vein thrombosis; Scr = screening; DC = discharge; AC = anticoagulation therapy; AF = atrial fibrillation; lipid = lipid-lowering medications; BP Meds = blood pressure medications; SMK Cessat = smoking cessation; DM Meds = diabetes mellitus medications.

Discussion

Improving the quality of stroke prevention and care is a global public health priority. Evidence-based therapeutic and preventive measures are available for ischemic stroke but remain significantly underused in China. GWTG-Stroke, a landmark American Heart Association/American Stroke Association initiative, showed substantial and sustained improvements, based

on predefined performance measures, on quality of stroke care and prevention in 790 US hospitals.¹⁰ Whether GWTG-Stroke is applicable outside the United States to benefit nations with different health care infrastructures and economies remains to be determined. Our study suggested that applying the GWTG-Stroke data collection and feedback procedures is feasible in a country that spends substantially less than the US does in health care dollars under a public health insurance program.

Patient characteristics, including stroke types and subtypes, and risk factor profiles were largely comparable between patients in Shanghai and those in the US GWTG-Stroke program. Delays in hospital arrival after the onset of stroke were considerable in Shanghai, where only 5 to 7 percent of patients arrived at the hospital within 2 hours of the onset of stroke symptoms. Nearly 50 percent of patients did not have clear information on either the time of onset of symptoms or the time of arrival at the hospital. These data suggest a need for increasing the public awareness of stroke signs and symptoms and for a timely response to stroke.

Early prescription of antithrombotic medications and prescription of antithrombotics on discharge both occurred at a lower rate for Shanghai patients compared with the rates for US patients. This could be attributed partly to local practice, which does not favor aggressive stroke prevention in patients with poor functional outcomes. This gap suggests that more rigorous adherence to this GWTG-Stroke guideline is needed, including aggressive treatment for those with poor functional outcomes, especially when more favorable outcomes were noted among patients who received antithrombotics on discharge than among those who did not.

The other performance measures show substantial disparity between this study and GWTG-Stroke. The most striking difference was use of IV tPA for those arriving within 3 hours of stroke onset: 4 percent in Shanghai versus 73 percent in GWTG-Stroke.⁹ Shanghai data also showed that only 2 percent of patients with ischemic stroke received IV tPA treatment. IV tPA is an important measure of the quality of stroke care and reflects the readiness of a stroke center to treat patients with stroke in an emergency setting with adequate facilities, staffing, and training. The relatively late arrival of patients with stroke is a likely cause of the low IV tPA rate. Only 5 to 7 percent of Shanghai patients with ischemic stroke arrived within 2 hours of stroke onset and in time for IV tPA treatment.

Shanghai needs more public education and more rigorous community outreach programs. Together, these findings suggest that stroke centers in Shanghai are far behind in fulfilling an important therapeutic measure in acute stroke care. This was especially the case when patients with ischemic stroke who arrived within 2 hours and received tPA experienced better functional outcomes compared with those who also arrived within 2 hours and did not receive tPA.

Anticoagulant treatment for patients with atrial fibrillation; prescription of medications for hyperlipidemia, hypertension, and diabetes; and counseling for smoking cessation were all given at a substantially lower rate for Shanghai patients than for US patients in the GWTG-Stroke program. This finding indicates that important preventive measures also need to be improved greatly in Shanghai.

After the implementation of the registry system, all quality-of-care indicators improved somewhat. This could be attributed mainly to the attention to care from physicians and nurses. This finding suggests that implementing such a program may indeed help improve the quality of care. Nevertheless, data collection and feedback are insufficient to achieve high levels of performance. Major barriers to data collection include difficulties in automating interfaces with the laboratory, imaging, and hospital health information systems. Thus, more manual data entry was required than anticipated because of increased resource requirements. In addition, barriers to interfacing with prehospital or emergency medical service systems impeded efforts to reduce prehospital delays in stroke treatment. Inconsistencies in data definitions and systems among hospitals will likely be a potential barrier to expansion of the registry to additional hospitals, and any future projects will need to address these issues at the outset.

In conclusion, implementing a registry system in Shanghai to support the Get With The Guidelines program to improve the quality of stroke care is feasible. This element of the larger program is critical to support a team-based quality improvement program in China with the expectation of improving stroke care quality and stroke outcomes. Also, public health interventions to raise awareness of the signs and symptoms of stroke, complemented by active improvement and integration of the components of systems of stroke care, are necessary to improve stroke outcomes in China.

Key Findings and Lessons Learned

- The delay in the time from the onset of ischemic stroke to arrival at the emergency department in Shanghai was considerable. The proportions of eligible ischemic stroke patients treated with tPA and given prescriptions for therapies for preventable conditions were considerably lower than in the West.
- After implementation of the new data system, major quality indicators improved.
- Implementation of a “Get With The Guidelines” program to improve the quality of stroke care is feasible, but considerable difficulties exist. These specifically involve hospital internal policies, conflict between the hospital information system and the registry data system, impossibility of automated data upload, and inconsistencies in data definitions and systems among hospitals.
- Public health interventions to raise the awareness of the signs and symptoms of stroke and to decrease the delay in seeking care, complemented by active improvement and integration of the components of systems of stroke care, are critical to raising survival rates from stroke in Shanghai.

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Encouraging Primary Care Physicians to Talk With Their Patients About Stroke Risk Factors: A Brief Intervention in Indonesia

Pamela A. Williams and Kenneth A. LaBresh

Introduction

In Indonesia and other low- and middle-income countries (LMICs) around the globe, stroke presents a huge burden of death, disability, and health care costs. Ischemic heart disease, cerebrovascular disease, and stroke together are the leading contributors to this global burden of death and disability.¹ Mortality rates from stroke are greater in LMICs than in high-income countries.² Stroke is the leading cause of death in Indonesia,³ accounting for approximately 15 percent of all deaths.⁴

Failure to assess and reduce the risk of stroke in patients seen in primary care practices is one reason for the greater stroke burden in LMICs than in high-income countries.² The Ministry of Health of Indonesia emphasized that community education is instrumental in addressing the increase in stroke and other noncommunicable diseases (NCDs) in its Strategic Plan.⁵ The Indonesian Neurological Association has established guidelines for stroke care across the care continuum from prevention to rehabilitation of stroke patients⁶; however, Indonesia has not established required stroke risk screening programs for primary care physicians to implement.

The leading modifiable risk factors for stroke are unhealthy diet, physical inactivity, smoking tobacco, hypertension, and overweight or obesity; collectively, these contribute 80 percent of stroke risk.² Not surprisingly, the prevalence of these risk factors is high in Indonesia. Percentages of Indonesians with such risk factors are as follows: low-fiber diet (94 percent), physical inactivity (42 percent), smoking (29 percent), hypertension (27 percent), and obesity (15 percent).⁷

Advice for patients on modifiable risk factors and improved screening practices, along with policy changes, are critical to lessen stroke burden in

Indonesia.^{8,9} In LMICs such as Indonesia, interventions that work within the primary health care system may provide optimal benefit and convenience.⁸ However, little is known about the stroke risk screening practices of primary care physicians in Indonesia and how they talk with patients about addressing their stroke risk factors through behavior changes.

This pilot project had two main objectives. The first was to learn about the current practices of primary care physicians in Indonesia and devise strategies to motivate them to screen patients and inform them about their stroke risk factors. The second was to test the impact of a brief intervention on the frequency with which physicians screen their patients to assess their risk for stroke and recommend risk-factor modifications.

Methods

Collaborators and Sites

We collaborated with in-country researchers from the School of Medicine at Gadjah Mada University (UGM) for all phases of the research. For the setting, we focused on *puskesmas*, free primary health care clinics located within each health district in Indonesia. *Puskesmas*, as the primary health facilities in the country's National Health Insurance program, provide comprehensive health services, including promotion, preventive, treatment, rehabilitation, obstetric, and medical emergency services. They are the first level of health service that patients seek for health care.¹⁰ We selected Yogyakarta City as our primary site because it has the second-highest diagnosed stroke prevalence in Indonesia (10.3 per million).¹¹

Study Phases

The study was carried out from July 2013 to April 2014. We first conducted focus groups with primary care physicians representing *puskesmas* in Yogyakarta City to gain a better understanding of their current stroke risk screening practices and to learn about the context to facilitate development of the intervention.¹² Then, based in part on these formative data, we developed the intervention and measured its impact on physicians' discussions with patients about their stroke risk and recommendations to modify their risk factors. Finally, we conducted limited in-depth interviews with the primary care physicians and nurses who conducted the intervention at the *puskesmas* to learn how to improve the intervention for the future.¹³

Focus Groups

We conducted three focus groups with a convenience sample of 23 physicians in Yogyakarta City, Indonesia, who work in *puskesmas*. The physicians who participated were mostly female (60 percent), with an average age of 33 years. They had been practicing medicine for an average of 7 years. Nearly three-quarters of them had not had formal stroke prevention training. Many also worked in private practice, other public clinics, or hospitals.

Intervention Study

We employed a quasi-experimental design, as the resources were not available to support random assignment of a sufficient number of clinics to treatment or comparison conditions to have adequate power to detect any treatment effects. Specifically, we selected an interrupted time-series design, involving multiple pretest and posttest observations at equal intervals of time over a 15-week period across four *puskesmas*.¹⁴ Each *puskesmas* received the intervention, but the timing of the start of the intervention and the number of data collection intervals varied over the 15-week period. We distributed the intervention materials for 8 weeks at each of the four *puskesmas*.

During the intervention, nurses placed a checklist of modifiable stroke risk factors (i.e., blood pressure, smoking, diet, body weight, physical activity) in physicians' charts for them to discuss with their patients. Nurses also gave patients a one-page educational worksheet covering the same list of stroke risk factors to complete in the waiting room before their appointment with the physician. During both intervention and nonintervention assessment weeks, trained interviewers conducted exit interviews with a total of 675 adult patients with no history of stroke immediately following their medical appointments to assess whether their physicians discussed with them their stroke risk factors and recommended behavior changes.

In-depth Interviews

We recruited a convenience sample of eight physicians and nurses who had administered the intervention (two per *puskesmas*) for one-on-one in-depth interviews to learn about their experiences with the intervention.

Results

Focus Groups

Findings from the focus groups provided important context for developing the intervention. Physician procedures for screening patients for stroke risk factors varied considerably. Physicians reported that they screened patients depending on patient appearance (e.g., yellowed teeth from smoking cigarettes), complaints, or the presence of other related risk factors (e.g., diabetes), rather than on risk for future events. Typically, healthy patients are not screened for modifiable risk factors.

The top barrier to physicians screening for stroke risk was lack of time during appointments. Each *puskemas* is staffed with three or four physicians who treat 80 to 150 patients within a 4-hour period, often meaning 5 to 10 minutes for the average physician consultation. Furthermore, care in the *puskemas* is structured so that a patient does not always see the same physician, which makes it challenging to monitor a patient's behaviors over time. Patients' limited education and physicians' beliefs that patients are reluctant to change their habits are also important obstacles.

Given these barriers, physicians said that the most appealing intervention approaches for them were those that were brief and easy to use, such as simple checklists. For patients, they recommended using stroke prevention education materials such as simple leaflets with common language and pictures or visuals, among other options.¹²

Intervention Study

The intervention did not increase the likelihood that physicians would discuss patients' risks for stroke in general. That is, it did not increase whether patients reported that the physician discussed their blood pressure, smoking status, fruit and vegetable intake, physical activity, or body weight (or some mix of these topics). It did, however, increase the likelihood that physicians would recommend that patients change their modifiable stroke risks. For example, patients affirmed that the physician recommended that they should lower their blood pressure. Physicians more frequently recommended that patients lower their blood pressure and get physical activity than they addressed other modifiable risk factors.

Based on data that patients reported in exit interviews, physicians are holding discussions with patients about their stroke risk factors less than half of the time (other than discussing their blood pressure levels).

Moreover, recommendations on modifying their stroke risk factors occur even less frequently. Williams and colleagues provide a full description of the intervention study methods and findings.¹³

In-depth Interviews

Nurses and physicians who implemented the intervention and participated in the interviews cited barriers to implementation. These obstacles included competing priorities, such as addressing health problems from volcanic ash. Such responsibilities increased their workload for only a few days, but the need to juggle these concerns serves as a reminder that volcanic eruptions and other environmental events are frequent in this part of Indonesia. Overcrowded facilities were another problem. For instance, in two of the four *puskesmas*, the physician and nurse were located in the same examination room because of the limited space. Poor motivation and lack of buy-in from physicians and nurses were yet other barriers.

Respondents reported that having limited numbers of staff was a challenge. For that reason, they focused on assessing risk only for patients perceived as having a very high risk for stroke, instead of for all patients (primary prevention) as the intervention had intended. They also reported that physicians and nurses were initially enthusiastic about implementing the intervention. Because health care is free at *puskesmas*, however, many patients come for care frequently. The arrival of repeat patients lessened the physicians' and nurses' motivation to repeat the intervention with these patients.

The interviewees made suggestions for future similar studies. One was to provide individual nurses and physicians with incentives (e.g., money), particularly incentives based on the number of patients served, to encourage them to implement the intervention. This study provided monetary incentives to each *puskesmas* only to offset time for participation in the study. Another was to have an assistant at each *puskesmas* to help patients complete the patient educational worksheet (e.g., elderly patients need assistance if they do not have their glasses). They also recommended that one physician at each *puskesmas* coordinate the study.

Discussion

Failure to screen patients in primary care and thereby reduce stroke risk is one reason for the disproportionate stroke burden in LMICs such as Indonesia.² Thus, improving the regularity of these practices is particularly important. Other experts have suggested that primary prevention interventions that use a comprehensive approach for improving common risk factors for NCDs via population-based approaches are the most cost-effective means for slowing their worsening.^{8,9} Given that stroke is the leading cause of death in Indonesia, which is the fourth most populous country in the world, interventions to improve screening and reduce risk hold considerable promise for reducing the burden of stroke and cardiovascular disease in this very large LMIC.^{3,15}

This study gathered important contextual information on the current stroke screening practices of primary care physicians who work in *puskesmas* in Yogyakarta City, Indonesia, and on the organizational environment of the *puskesmas*. We found that a brief intervention to motivate *puskesmas*' physicians raised the likelihood that they would recommend that patients change their modifiable stroke risks. However, getting primary care physicians and nurses at *puskesmas* to conduct even a brief intervention consistently was difficult, although they had been trained on the brief intervention. Physicians often did not routinely discuss and make recommendations on modifying patient stroke risk factors, as we had envisioned.

This outcome was not entirely surprising, because successful implementation of interventions often requires synergy among patients, physicians, and organizations.¹⁶ Indonesia does not have established stroke risk screening programs that give priority to conducting primary stroke prevention in primary care facilities. The intervention that we put in place represented a significant change from the usual care delivered by *puskesmas*' physicians, despite our efforts to make it brief. Further organizational barriers included lack of time, resources, and established systems for stroke risk assessment, using the resources available in the *puskesmas*.

Physician and nurse attitudes, including lack of motivation and the inertia of usual care routines, also played a role. During focus groups, physicians often reported that patients were "stubborn" about modifying their risk behaviors. This indicated that physicians may believe that talking with patients about their risk factors will not change patient behaviors. It may also reflect that physicians do not feel confident in their skills to discuss behavior change with patients.^{17,18} These knowledge, organizational, and attitudinal barriers

are common barriers to physician adherence to practice guidelines related to behavior change.^{18,19}

Future implementations of the intervention should address these barriers. First, training for physicians, such as motivational interviewing, could support them in overcoming **knowledge** barriers. Second, nurses and physicians who carried out the intervention suggested that providing incentives (e.g., money) for physicians and nurses, particularly based on the number of patients served, could tackle some of the **attitudinal** barriers. This study provided incentives to each *puskesmas* only to offset time for research participation. Certainly, offering reimbursement or other incentives is an organizational strategy that can address these types of barriers.¹⁶ Third, providing educational materials that physicians can give patients, establishing champions at each *puskesmas* who serve as role models for physicians, and shifting some physician responsibilities to other staff may help overcome some of the **organizational** barriers to delivering primary prevention stroke screening services. Fourth, identifying risk factors before a primary care visit could reduce the burden that *puskesmas* physicians face both to screen patients and to provide treatment and recommendations to reduce their risk. Finally, implementing programs to redesign clinical workflows and better use ancillary staff may help physicians to focus on providing specific recommendations and motivation for patients to change behaviors associated with increased risk for stroke.²⁰

Through this pilot study, we gained insight into the way the Indonesian health system functions and a better sense of the feasibility of interventions within the system. Despite partnering with an in-country collaborator and conducting formative focus groups with physicians in *puskesmas* before developing and implementing the intervention, we learned additional lessons through implementing the intervention study and conducting follow-up interviews. The latter, in particular, were an important source of information about the medical practice environment, which in turn could be used to design more comprehensive and larger-scale interventions.

A larger follow-up study could address many of the barriers we identified. These especially include finding ways to provide physicians with more organizational supports. Such assistance permits clinicians to spend more time with patients and fosters greater accountability for preventive practices, such as occurs now in private practice clinics. Conducting such a study in a different health care setting in Indonesia would allow researchers to isolate the role of the systemic differences between two delivery models (*puskesmas* versus private practice) and could help ascertain what changes are possible.

Based on this pilot work, potential next steps include conducting a similar intervention in a setting in which physicians have more environmental and system supports, such as those that exist in private practice clinics. Addressing these larger environmental and organizational barriers is important as part of a more comprehensive project that could address stroke risk screening and targeted interventions to modify stroke risk factors in health care settings in Indonesia. Such a project has the potential to reduce future disease burden for stroke and other cardiovascular diseases.

The findings from this project reinforce the concept that the barriers in one setting may not generalize to another setting without modifications to address them.¹⁸ This is especially true when embarking on a study in a country with a different health care system and its own unique challenges. Nonetheless, for stroke prevention in particular and prevention of NCDs in general, overcoming these barriers is crucial. In the current context of global health, stroke cannot be considered in isolation; rather it should be seen as a major component of prominent NCDs including cerebrovascular diseases, cancers, chronic respiratory diseases, and diabetes mellitus.¹ In Indonesia, the prevalence of the leading modifiable risk factors for stroke is high, including hypertension, smoking tobacco, overweight or obesity, unhealthy diet, and physical inactivity⁷; these are also risk factors for other leading NCDs. The United Nations declaration to reduce premature death attributable to NCDs by 25 percent by 2025 included targets of relative reductions in each of the behaviors targeted in this intervention for stroke prevention.²¹ These behaviors are important for NCD prevention in general.

Conclusion

With this pilot project, we aimed to learn the current stroke screening practices of primary care physicians who work in *puskesmas* in Indonesia. We wanted insight into intervention strategies that we could use to motivate physicians to talk with their patients about stroke risk factors. We developed and tested the feasibility and impact of implementing a brief intervention in *puskesmas*. Finally, we asked for feedback from physicians and nurses who implemented the intervention to improve future implementation of the intervention.

We learned that physicians do not routinely screen patients on their stroke risk factors. Limited time with patients and the belief that patients often do not change their risk behaviors were key barriers to doing so. We found that a

brief intervention in *puskesmas*, consisting of a checklist of modifiable stroke risk factors for physicians and a patient education worksheet on the same risk factors, can increase the likelihood of physicians' recommending that patients change their modifiable stroke risks. Nevertheless, physicians often did not routinely discuss and make recommendations for modifying patient stroke risk factors, as we had envisioned.

The intervention may need to develop support for physicians—such as medical training, educational materials for patients, champions who serve as role models, and health care system supports that shift some of their responsibilities to other staff. In these ways, programs can realize their full potential and address the barriers to intervention implementation that this study identified.

Key Findings and Lessons Learned

- Primary care physicians in *puskesmas* in Indonesia do not routinely screen patients on their modifiable stroke risk factors (primary prevention).
- A brief intervention conducted in *puskesmas* increased the likelihood of physicians' recommending that patients change their modifiable stroke risks (lower blood pressure, eat more fruits and vegetables, get exercise, and lose weight).
- Physicians and nurses did not consistently implement the intervention during the study.
- Addressing barriers to implementing the intervention, particularly related to physicians' knowledge and attitudes and to the health care organization, is crucial to improve the consistency of implementation and (likely) the intervention's impact.

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Deciphering Chronic Kidney Disease of Unknown Etiology in Sri Lanka

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Introduction and Background

Geographic Setting

Sri Lanka is an ethnically, culturally, and geographically diverse island nation located in the northern Indian Ocean off the coast of India. Although the country has many urban areas, the vast majority of its 20 million people reside in rural settings. Sri Lanka has recently transitioned from a low- to a middle-income nation and is undergoing a significant demographic shift. It has a large young population, but it also has one of the largest elderly populations in the developing world. The average life expectancy is now greater than 75 years and rising.

Sri Lanka maintains one of the strongest public health systems in developing Asia. The system is built on a foundation of community-based medical doctors, a network of mobile midwives and environmental health officers, and a commitment to investing in public health research and training. Similar to other recently established middle-income countries, the disease pattern has shifted away from infectious, maternal, and childhood concerns toward noncommunicable diseases (NCDs).

Noncommunicable Disease Burden

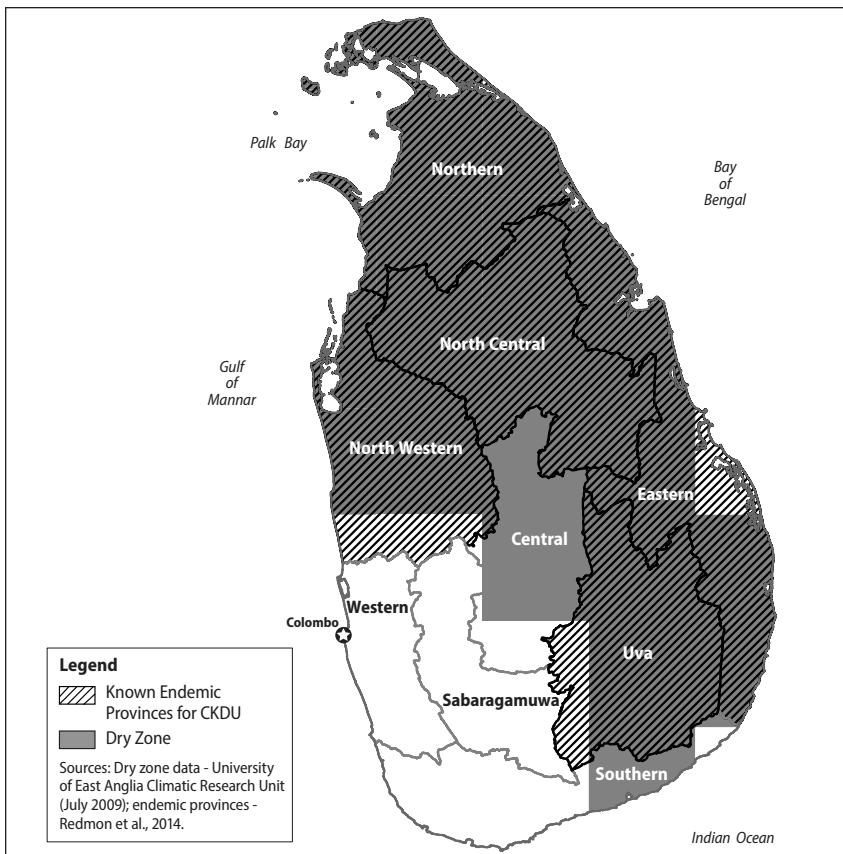
NCDs currently account for nearly 90 percent of the overall disease burden in Sri Lanka.¹ An increasing proportion of the Sri Lankan population is affected by NCDs attributable to several suspected factors; these include a rapidly changing age distribution, economic development, urbanization, reduced levels of physical activity, a decline in healthy eating patterns, and tobacco, alcohol, and substance use and abuse. NCDs are often perceived

to be associated with affluent lifestyles, but they are also a burden for more impoverished areas of Sri Lanka. The prevalence of hypertension, for example, does not show a significant difference between the lowest and highest wealth groups.

The Chronic Kidney Disease of Unknown Etiology Epidemic

A rapidly growing facet of the NCD disease burden is chronic kidney disease (CKD). What is particularly perplexing is that CKD of unknown etiology (CKDu) is causing a public health epidemic in Sri Lanka and other developing countries with rural agriculture. These cases are concentrated in the North Central Province but are found throughout Sri Lanka's dry zone, which gets approximately 3.6 to 50 mm of precipitation annually (Figure 7.1).

Figure 7.1 Provinces in the dry zones of Sri Lanka are affected by chronic kidney disease of unknown etiology



Since the early 1990s, the number of CKDu cases has risen appreciably; about 2,000 new patients seek treatment annually in Sri Lanka. Overall, approximately 20,000 to 22,000 individuals are affected. Approximately 8,000 CKDu patients are under treatment in endemic areas.^{2,3}

Diagnosing CKDu

Patients diagnosed with CKDu have CKD with a typical HbA1C below 6.5 percent (not diabetic), blood pressure below 160/100 mm Hg untreated or below 140/90 mm Hg on up to two antihypertensive medications (not hypertensive), and no history of snake bite or other known risk factors associated with traditional CKD.⁴ The consensus is that CKDu in Sri Lanka is asymptomatic in early stages but slowly progresses until late stages, when symptoms appear and the disease is characterized by renal tubular and interstitial damage. CKDu is present among both sexes, but more patients are men (especially those aged 30 to 60 years), the majority of late-stage cases are observed in men, and men appear to have the most severe cases.⁵⁻⁷

Searching for CKDu Risk Factors

The causes of CKDu genesis and progression are likely multifaceted. Potential risk factors hypothesized or reported include environmental exposure to nephrotoxins, agricultural work, diet and nutrition, dehydration, lifestyle factors, and genetic susceptibility.^{8,9} The disease is slowly progressive and takes many years for symptoms such as fatigue, panting, nausea, anemia, and severe pain to develop. Upon diagnosis, the impact is traumatic for patients and their families, who are often unable to pay the high direct and indirect costs of the renal dialysis treatments necessary to prolong life.¹⁰

Within endemic areas, CKDu has affected primarily people of lower socioeconomic status who reside in agricultural areas or engage directly in farming. The World Health Organization (WHO) estimates that 15 percent of the region's population of 2.5 million is at risk. CKDu is requiring an increasingly larger proportion of limited health care budgets, and the potential risk factors associated with it are not yet understood well enough for educational awareness and prevention efforts to be effective.^{2,3} Furthermore, the number of individuals with CKDu is likely underreported because of the lack of symptoms prior to advanced stages, the high costs associated with medical care, and the limited number of dialysis clinics.

CKDu Hot Spots Around the Globe

Geographical hot spots of CKDu have emerged in numerous countries spanning the globe. Rural inhabitants of Central America, including those in localized geographical areas within El Salvador, Nicaragua, and Mexico, have experienced a rapidly expanding CKDu epidemic since 2000.¹¹⁻¹⁴ CKDu in Central America is prevalent among young male agricultural workers engaged in sugarcane or cotton farming under very hot conditions. Patients experience a progressive, asymptomatic decline in kidney function, as measured by estimated glomerular filtration rate (eGFR).¹⁵⁻¹⁸ Other important hot spots include India, where the disease pattern appears similar to that observed in Central America, and Tunisia, Serbia, Bulgaria, Croatia, and other localized areas within the Balkan Peninsula, where thousands of people have been affected.¹⁹⁻²²

Project Collaboration Background

The size and scope of this emerging Sri Lankan health crisis prompted Professor Ananda Rajitha Wickremasinghe from the University of Kelaniya's Department of Public Health to initiate contact with RTI and formally ask whether RTI's advanced analytical skills and instrumentation could be used to obtain laboratory analytical results for biological and environmental samples that had already been collected in selected CKDu-endemic areas of Sri Lanka. A cross-disciplinary team of RTI technical staff collaborated to evaluate how the current sample repository could be analyzed at RTI; the data were subsequently used to characterize further potential CKDu risk factors and provide additional insight into the necessary structure of a more comprehensive follow-up study on CKDu.

Based on the research reviewed and regional geochemical analysis study, we explored recommendations for developing a more comprehensive and definitive way to identify CKDu risk factors in a subsequent study. We also identified how CKDu could be mitigated once the risk factors are more clearly established.

Methods

Baseline Literature Review

The RTI team first conducted a comprehensive literature review on CKDu in Sri Lanka to identify data gaps. The review included evaluating both focused studies that hypothesized that a single risk factor may be related to CKDu

and a broader study that made an effort to approach the causes of the CKDu epidemic in Sri Lanka from a multifactorial standpoint.

The emerging CKDu crisis in Sri Lanka prompted a variety of investigations to determine the scope and causes of the disease. The broad research topics studied thus far include fertilizers with metal contaminants; pesticides, including organophosphates and glyphosate; mycotoxins, including ochratoxin A; hydrogeochemistry, including fluoride in water; and cookware and cooking practices. Our summary describes the findings of both highly focused studies and more broadly focused studies.

Focused Studies

In an effort to determine both the extent and potential risk factors of CKDu in Sri Lanka's North Central Province, researchers have recently conducted several etiological studies.³ Cadmium is a known nephrotoxin and has caused environmental contamination resulting from the application of some inorganic, phosphate-based fertilizers.^{25,26} Studies have reported renal tubular dysfunction following environmental exposure to cadmium elsewhere in Asia.^{27,28} As rice and freshwater fish are important components of the Sri Lankan diet,²⁹ several studies explored cadmium levels in these media obtained from endemic area irrigation and drinking waters.³⁰⁻³³ Other investigations have explored potential CKDu linkages with exposure to acetylcholinesterase (AChE)-inhibiting organophosphate pesticides or metal-chelating glyphosate broad-spectrum herbicides.^{34,35}

The historic use of arsenic-containing pesticides has also prompted studies on the potential exposure to this element and the genesis of CKDu.³⁶ Other laboratory studies estimated the presence of nephrotoxic mycotoxins, including ochratoxin A, in food and CKDu patients within the endemic area or the deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme protecting against oxidative stress.^{8,37} Ayurvedic medicines have also been cited as a potential factor in the genesis and progression of CKDu because of their high prevalence in Sri Lanka.³⁸

In addition to its potential exposure from agrochemical-based nephrotoxins, Sri Lanka's CKDu-endemic area is within the country's dry zone (see Figure 7.1), which is characterized by a unique, complex hydrogeochemistry. Alternating wet and dry cycles can affect soil redox potential and other physiochemical characteristics (e.g., organic matter, pH, conductivity, cation exchange capacity) that determine heavy metal mobility and bioavailability. Also within the endemic area are regions with moderate to

highly elevated fluoride content in their groundwater.³⁹ This phenomenon has prompted some investigators to speculate that elevated levels of this analyte, in combination with other factors, including the leaching of aluminum from low-grade cookware, can contribute to the genesis of CKDu.^{40,41}

The tubulointerstitial progression of CKDu and its prevalence in the agricultural dry zone of Sri Lanka spurred many narrowly focused investigations seeking to identify population susceptibility or the presence of one or more environmental nephrotoxins, specifically agrochemical contaminants. However, because most studies focused on one potential CKDu risk factor, many studies involved small sample sizes, dated field collection or laboratory analytical methods, or incomplete media studied (e.g., biological, environmental, food). Study conclusions are therefore often difficult to replicate, resulting in more questions than answers.

Broader Study

The most comprehensive study undertaken on the CKDu issue in Sri Lanka was the product of a collaborative effort between the Ministry of Health (MoH) and WHO. This case-control study was conducted from 2009 through 2012 and sought to determine the prevalence and risk factors of CKDu in the endemic area; it featured heavy metal, pesticide, and biochemical measurements of biological and environmental samples. The biological sample types included urine, blood serum, hair, and nails. The environmental sample types included water, food (e.g., rice, vegetables, and fish), fodder (e.g., pasture, weeds), tobacco, pesticides, and fertilizer. Although the investigators collected samples for each of these sample media, the number of samples varied by media type. As an example, biological samples included 733 CKDu cases, but between 57 and 495 individuals were chosen for urine, serum, hair, and nail samples; most individuals were tested only for three heavy metal constituents. The environmental samples also varied in collection size and analysis procedures. For example, 119 food samples were collected from endemic areas and 32 were collected from nonendemic areas, whereas 88 soil samples were collected from endemic areas and 41 samples from nonendemic areas.

This study reached two conclusions. First, chronic exposure to low levels of cadmium through the consumption of contaminated food and water is a risk factor in how CKDu develops. Second, selenium deficiency and genetic susceptibility may also be predisposing factors.⁴²

Although the MoH and WHO collaborative study represented an early multifaceted effort to identify the risk factors of CKDu in Sri Lanka, the findings have been controversial, and many questions remain unanswered.⁴¹ Based on the critical analysis of the Sri Lankan MoH-WHO study, we recommended (in a previously published paper²³) doing the following:

1. Further evaluate the CKDu case definition and refine medical testing procedures, as needed.
2. Geospatially link biological and environmental samples.
3. Provide more comprehensive information on the overall study design and field protocols.
4. Provide more comprehensive information on the laboratory protocols.
5. Publish additional studies on CKDu in Sri Lanka and integrate the findings.

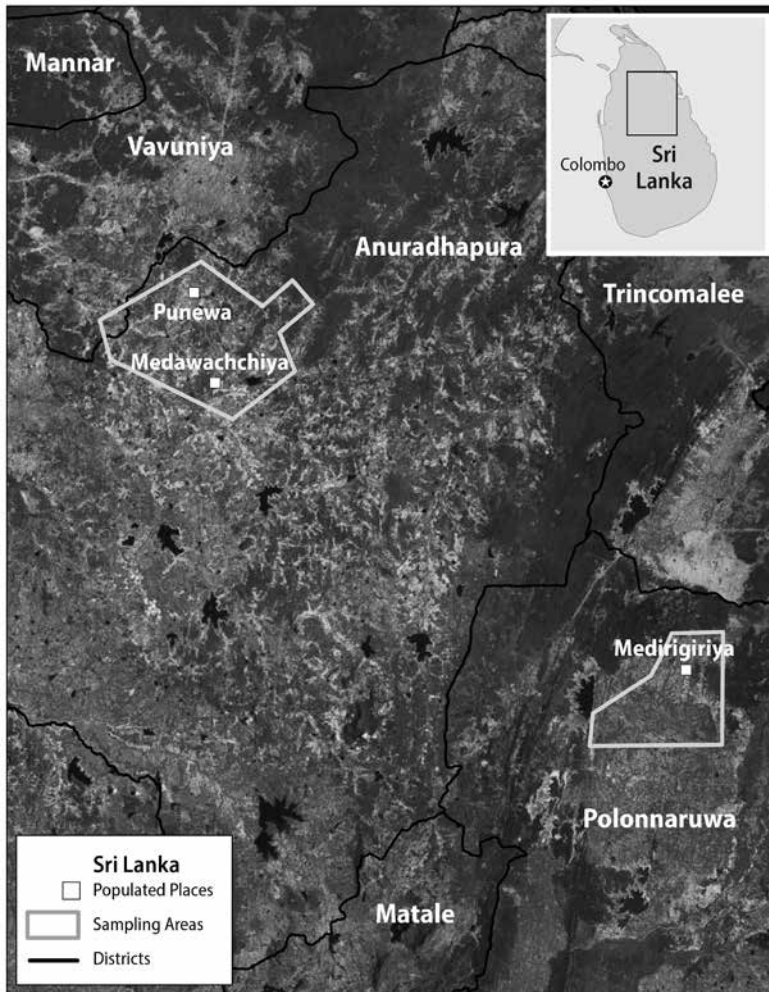
These critical analyses identified several potentially significant study design flaws.²³ Some observers have claimed that the conclusions were “predetermined” in response to enormous political and economic pressure applied by the agrochemical industry.⁴³

Data Gathering and Partnership

Before RTI's involvement, field research design, brief participant interviews, and sample collection had been completed in 2012 and 2013 through a partnership between the Faculty of Medicine, University of Kelaniya (Sri Lanka); the Faculty of Medical Sciences, University of Sri Jayewardenepura (Sri Lanka); the University of Alabama at Birmingham's Department of Epidemiology (USA); and the Sri Lanka Atomic Energy Authority. The Sri Lankan collaborators conducted field design and completed sample collection in 2012 and 2013.

The Institutional Review Board of the University of Kelaniya approved informed consent and study protocols. The investigators collected a repository containing biological samples, including blood and hair, and supporting environmental media, including regional freshwater fish, locally harvested rice, drinking water, and soil samples, from CKDu cases and non-CKDu controls in endemic areas. The towns of Medawachchiya and Medirigiriya were the study sites within the North Central Province endemic area (Figure 7.2).

Figure 7.2 Sampling areas in two endemic dry zone regions of Sri Lanka



In response to the scope of the CKDu crisis and the lack of consensus concerning the MoH-WHO collaborative study findings, RTI and Sri Lankan collaborators formed a partnership in late 2013.²⁴ RTI personnel subsequently traveled to Sri Lanka for a data-gathering trip with university partners; the main goals were to gather general insight on the current knowledge of CKDu in the population and to arrange for transport of the sample repository and associated data to RTI International in Research Triangle Park, North Carolina, USA, for subsequent laboratory analysis.

The study collected biological samples from men ages 29 to 62 living in the North Central Province region. Environmental samples came from the environs of the study participants' residences, and local rice farmers and fishermen in the general north Central Province region provided food samples. Some individuals were undergoing ongoing medical treatment for CKDu; the diagnosis was confirmed in living patients by small, echogenic kidneys, elevated serum creatinine levels, and the presence of proteinuria via dipstick urine test without hypertension, diabetes, or other renal disease at the time of diagnosis. Controls were individuals living within the study areas but who had no biochemical evidence of CKDu.

Laboratory and Data Analysis

Following sample transport, RTI completed the advanced, blinded laboratory analyses at its headquarters in Research Triangle Park, North Carolina, between November 2013 and March 2014. The RTI Institutional Review Board approved the protocol.

The sample repository included three media types: environmental (soil and water), biological (blood), and food (rice and fish). RTI scientists analyzed the samples for targeted analyte concentrations using an array of state-of-the-art instrumentation; we sought to determine the concentration of a suite of heavy metals and additional trace elements and ions linked with CKDu in literature reports and other elements of interest. Appropriate quality control samples were processed along with study samples to ensure a high level of data quality. Collection of scientifically defensible data is critical because many published reports on this topic have been challenged on the grounds of irreproducible data and inadequate protocols. Additionally, RTI laboratories have extensive experience with measurement equipment that is not available to CKDu researchers in Sri Lanka.

We used a sensitive, broad-panel metallomics and mineralomics approach to generate geochemical laboratory analytical data. These data allowed us to determine whether the regional mean and maximum levels of these constituents in the CKDu endemic area are of potential concern in comparison with risk screening levels or published mean and maximum values. These advanced laboratory analyses addressed some of the controversial nephrotoxin findings in the MoH-WHO collaborative effort. Specifically, the analyte suite included up to 18 metals and minerals, including cadmium, arsenic, selenium, and fluoride. We used advanced sample preparation (cleanroom facility and

high-purity reagents) and analysis instrumentation. These techniques included inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectrometry (ICP-OES), ion chromatography (IC), and combustion atomic absorption spectrometry (CAAS).

Staff analyzed several laboratory QC samples with a sample batch. Method blank data consistently indicated that analyte background contribution from the employed reagents and procedures was not significant.

Results

We conducted a regional geochemical analysis of the RTI laboratory analytical data by conducting basic statistics that identify the constituent concentration mean, minimum, and maximum values for the multimedia samples collected. We compared these values against other publicly available risk screening data (e.g., for soil and water) or published values (e.g., for blood). We also reviewed the data gaps in the current sample repository and recommended the completion of a comprehensive multimedia and georeferenced sample collection with associated survey information in a follow-up study.

The objective of this limited geochemical laboratory analysis was to determine the concentration of metals and trace element nutrients in biological samples (human whole blood and hair), food samples (fish and rice), and environmental samples (drinking water and soil). We quantified the geochemical concentrations in biological and environmental media and subsequently used basic statistical measurements to compare media against applicable benchmark values, such as US soil screening levels. Laboratory analytical findings for the biological, food, and environmental study samples from Levine et al.²⁴ include the following findings:

- **Blood:** Cadmium and lead blood concentrations exceeded mean US reference values from healthy nonsmokers for 68.7 percent and 89.2 percent of the samples, respectively.
- **Hair:** Mercury levels in hair exceeded US mean reference values in 60.7 percent of the samples.
- **Rice:** The maximum measured cadmium concentration in rice is below the Codex Alimentarius Commission reference level and maximum allowable concentration for Chinese rice.

- **Fish:** Observed concentrations were similar to or lower than other recent literature reports.^{33,42} However, this sample size was limited and not directly linked to consumption habits.
- **Soil:** Arsenic, chromium, copper, iron, mercury, manganese, nickel, lead, and selenium concentrations exceeded mean background US soil concentrations. Within the limited number of soil samples, arsenic levels were determined to be above initial risk screening and mean background concentration reference levels.
- **Drinking Water:** Fluorine, iron, manganese, sodium, and lead exceeded applicable drinking water standards in some cases. Analyses revealed elevated fluorine levels, and many samples had “hard” or “very hard” water.

These biological data suggest that the population within the North Central Province is subject to chronic low-level exposure to cadmium, lead, and mercury. Analysts did not find that food samples exceeded reference values or standards. However, rice and freshwater fish are both important components of the Sri Lankan diet. Thus, given the relatively small number of samples collected from this limited study and the amount of these dietary food staples ingested, chronic exposure to cadmium could act as an environmental nephrotoxin. Accordingly, we recommend ongoing monitoring of these and other food staples in any subsequent laboratory analytical analysis designed to capture data that can be used to evaluate potential CKDu risk factors.

Environmental samples exceeded reference values and risk screening standards in certain cases, including arsenic, chromium, copper, iron, mercury, manganese, nickel, lead, and selenium in soils, and fluorine, iron, manganese, sodium, and lead in water. Overall, data collected from study drinking water samples reflected the unique hydrogeochemistry of the region, including elevated levels of several elements (e.g., fluorine and iron) and the prevalence of hard or very hard water.

We presented our findings at the US Environmental Protection Agency’s National Institute of Environmental Health Sciences at Research Triangle Park. We also provided educational awareness, a critique of the MoH-WHO study, and a summary of our laboratory analytical results in three separate papers.^{10,23,24}

Discussion

Studies to date have focused on a variety of potential risk factors for CKDu in Sri Lanka and other CKDu hot spots. The goals of our limited regional geochemical analysis study were twofold: (1) to complete broad panel element analyses of biological (human whole blood and hair), food (rice and freshwater fish), and environmental (soil and drinking water) samples collected from the CKDu-endemic area in Sri Lanka's North Central Province and (2) to use the data from this regional geochemical analysis to inform future multifactorial investigations regarding CKDu risk factors.

Our team focused on publishing a study analyzing a limited set of multimedia biological and environmental samples. Our aim was to identify whether metals or fluoride may be present above average levels based on standard health benchmarks and population averages. Given the relatively small sample size of this study, we could not definitively identify any single hydrogeochemical condition, environmental nephrotoxin, biochemical parameter, or other regional geochemical risk factor that could be linked to CKDu.

This preliminary screening identified that specific constituents may be present above levels of concern, but it did not compare results against specific kidney toxicity values or cumulative risk related to a multifactorial disease process. The data from this limited investigation are intended to be used in the subsequent study design of a comprehensive and multifactorial etiological study of CKDu risk factors that includes sample collection, individual surveys, and laboratory analyses to comprehensively evaluate the potential environmental, behavioral, genetic, and lifestyle risk factors associated with CKDu.

The complex nature of the unfolding CKDu health crisis in Sri Lanka and the significant remaining data gaps necessitate a multidisciplinary large-scale study. The etiology of CKDu is likely related to multiple risk factors including genetic predisposition, nutritional, behavioral and lifestyle factors, and exposure to one or more environmental nephrotoxins.

Conceptual Model

In Figure 7.3, we present a potential conceptual study model based on research conducted to date. This framework is organized by source; release, fate, and transport mechanisms; exposure media; exposure route; and human receptors.

Figure 7.3 Potential conceptual study model for CKDu risk factors

Potential Source	Potential Release, Fate and Transport Mechanisms	Potential Exposure Media	Potential Exposure Route	Potential Human Receptors
Agrochemical Application (e.g. potential heavy metal content within fertilizer or pesticide) Other Environmental Factors (e.g. industrial emissions, naturally occurring metals)	Particulate Emissions or Volatilization	Air	Inhalation	Agricultural Workers (e.g. middle-aged males)
	Dispersion and Deposition	Soil	• Ingestion • Dermal Contact	
	Uptake or Bioaccumulation	Food	Ingestion	
	Leaching	Groundwater	Ingestion	
	Runoff	Surface Water	• Ingestion • Dermal Contact	
	Erosion	Sediment	Ingestion	
Low Quality Cookware	Leaching	Food	Ingestion	Residents (e.g. children)
Traditional Ayurvedic Medicines (e.g. byproducts)	Medicinal Administration	Medicine		
Recreational Substances	Consumption	Alcohol or Tobacco		
Other Lifestyle Factors (e.g. over- and under-nutrition)	Variable	Variable		

This conceptual study model presents an example of the sources, media, and exposure pathways to consider. Nevertheless, it may change based on additional evaluation or new research findings. Researchers could evaluate potential mechanisms of action for CKDu genesis and progression based on the various risk-factor hypotheses. For example, metal nephrotoxins are often cited as potential concerns associated with agrochemical use, whereas generalized kidney stress may be related to lifestyle or behavioral factors such as dehydration and undernutrition.

A critical component of this approach is collecting data to obtain a better understanding of occupational, nutritional, hydration, and behavioral habits for agricultural workers and residents. In future studies, we also recommend including an in-depth survey questionnaire that considers demographic, lifestyle, and behavioral factors as potential additional exposure routes and media (e.g., tobacco use, vegetable consumption, and potential occupational exposures). Doing so will create a more robust informational dataset linked to laboratory analyses and let investigators consider cumulative exposures more fully.

Georeferenced Study Location and Receptor Population

To maximize the impact of robust data and appropriate interpretation, we propose two key actions: (1) any subsequent investigation should be conducted at “hot spot” locations within the endemic area in Sri Lanka, and (2) control groups should ideally consist of both asymptomatic villages within the endemic area and villages from nonendemic areas. Additionally, studies should link all multimedia sample data directly to field questionnaire information by sample identification and georeferenced location. As noted in Redmon et al., an approach that includes multimedia sampling and analysis along with georeferencing allows for more rigorous comparative data analysis, multivariate linear regression modeling, and human health risk assessment that will decrease the overall uncertainty associated with the corresponding results.²³

Further refining the CKDu case definition, developing an early diagnostic technique, and determining which geographic areas and hydrogeochemical parameters to include will also be critical in further differentiating endemic and nonendemic areas in the region. Lastly, efforts should be made to identify causal commonalities between CKDu in Sri Lanka and CKDu hot spots elsewhere in the world.

Quality Control

Another critical facet of future CKDu studies is early implementation of rigorous quality control procedures for both field sample and questionnaire data collection and laboratory analyses. Researchers should use both standardized protocols and advanced equipment and analytical methods to collect samples in the field and analyze them in the laboratory.

In studies to date, using inconsistent quality control procedures has complicated efforts to replicate study findings and has contributed to an atmosphere of distrust. Employing advanced sample preparation and analysis instrumentation with adequate sensitivity and resolution power to determine analytes of interest is critical, as are open and transparent quality-control procedures with a priori defined acceptance criteria. These protocols will bolster confidence in study findings within the scientific community and for the public at large.

Using a secondary, independent testing laboratory to prepare and analyze duplicate samples to compare analyte results is also important. Testing may focus on heavy metals, pesticide residues, genetic susceptibility, and biomarkers in biological and environmental samples. Implementing this step will provide further credibility to the results.

Data Evaluation

Laboratory analytical results and survey information should be evaluated using appropriate statistical analyses, which can include multivariate linear regression modeling if the sample size is sufficient. Additionally, a multimedia human health risk analysis could be conducted using concentration data obtained through field study collection and subsequent laboratory analysis and survey information about demographics, behaviors, and lifestyle factors. This knowledge base would enable investigators to model average and high health risk estimates associated with exposure to environmental nephrotoxins.

Similar studies could be implemented in other CKDu-affected countries to identify cross-country linkages. Ideally, a multicountry study could implement the same field collection, survey collection, and laboratory analytical techniques in CKDu-affected areas in two or more countries to identify and compare risk factors that contribute to CKDu incidence by country (Table 7.1).

Table 7.1 Post-field collection data evaluation and synthesis

- Conduct state-of-the-science laboratory analyses.
 - Perform statistical analyses to identify linkages and conduct multimedia human health risk analysis.
 - Perform similar CKDu studies in other affected countries.
 - Based on results, provide educational awareness and occupational health and safety training.
-

Source: Adapted from Elledge et al. (2014).¹⁰

Educational Awareness and Training

Expanded CKDu education access and coverage are desperately needed to address fears and aid in early detection. Current programs designed to reach high-risk and endemic communities are now under-resourced. Far too many patients are unable to access care and treatment consistently. Building the capacity of both the public health system and supporting testing laboratories in terms of equipment and professional staff training will be crucial components in the ongoing struggle against CKDu.

Providing educational awareness and occupational health and safety training to residents and public health providers will be critical within the endemic area and across Sri Lanka once researchers have unequivocally identified CKDu risk factors. Educators can base informational materials and educational or occupational training programs in Sri Lanka on the findings of a comprehensive field study to pinpoint the risk factors associated with CKDu.

Identifying risk factors, encouraging better processes of diagnosis and treatment, and fostering improvement in health outcomes in endemic areas will require a robust decision-support approach, as well as working across health, agriculture, and environmental agencies. Effective educational awareness and occupational health and safety training about mitigating the risk associated with CKDu can also be extended to health workers in other countries with increasing CKDu prevalence once risk factors are more clearly identified.

Global Implications

Identifying commonalities between the CKDu epidemic in Sri Lanka and similar CKDu health crises across the world is important. Table 7.2 outlines key next steps in a global effort to deal with CKDu. Global health research

Table 7.2 Important next steps for research and program development globally

- Share information as a public service and for research purposes.
 - Strengthen disease registries and surveillance reporting systems for cases of CKDu.
 - Develop capacity in national environmental toxicology and epidemiological networks, including the expansion and harmonization of laboratory equipment, protocols, and training to ensure data quality.
 - Prepare an economic evaluation of CKDu to model the costs and societal impact in Sri Lanka and elsewhere to support CKDu advocacy.
 - Evaluate and recognize the societal and economic impacts on communities and the nation as a whole.
-

collaborations by professional and medical staff that would facilitate data exchange and provide training in countries affected by CKDu would benefit patients and public health systems in Sri Lanka, India, North Africa, Central America, and the Balkan Peninsula. Given the complexity of the CKDu issue, international multidisciplinary collaborations will be necessary to facilitate research and help to implement policy actions and community outreach designed to mitigate CKDu risks. To be successful, these collaborations must consider political sensitivities and complexities within the study county and seek to identify one or more in-country champions.

Conclusions

The present burden of CKDu on the economy, the public health system, and families within affected communities is tremendous. The complexity and multifaceted nature of the emerging CKDu health crisis in Sri Lanka requires an interdisciplinary approach to identify the risk factors associated with CKDu and subsequently to achieve tangible, lasting improvement in health outcomes.

Key Findings and Lessons Learned

- Based on our study results and a review of current literature, we postulate that exposure to one or more environmental factors, coupled with behavioral or lifestyle conditions and a genetic predisposition of susceptible populations, may ultimately be responsible for CKDu genesis and progression.
- Given the relatively small sample size of this study, we could not definitively identify any single hydrogeochemical condition, environmental nephrotoxin, biochemical parameter, or other regional geochemical risk factor that could be linked to CKDu.
- This preliminary screening identified that specific constituents may be present above levels of concern, but it did not compare results against specific kidney toxicity values or cumulative risk related to a multifactorial disease process.
- Our limited regional geochemical analysis was conducted to inform study design for a potential subsequent multifactorial investigation that will allow for more intensive statistical measurements, risk analysis, and modeling to improve the likelihood of identifying multiple CKDu risk factors.
- The complex, multifaceted nature of the unfolding CKDu health crisis in Sri Lanka and the significant remaining data gaps necessitate a multifaceted, large-scale comprehensive study.
- RTI is well positioned as a multidisciplinary nonprofit research institute to collaborate with in-country investigators, clinicians, and policy makers to conduct a follow-up comprehensive study to decipher the risk factors associated with CKDu, and then subsequently provide educational and international development support.

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RTI International Grand Challenge: Improving Outcomes of Noncommunicable Diseases—What Did We Learn?

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Overview

The studies funded by this RTI International Grand Challenge program explored a range of interventions across diverse noncommunicable diseases (NCDs) and NCD risk factors in multiple countries in Asia (specifically, China, India, Indonesia, and Sri Lanka). Although the pilot studies described in Chapters 1 through 7 were conducted on a small scale, they did collect information that will be key for future efforts to improve patient outcomes from NCDs in low- and middle-income countries (LMICs). Such information includes identifying best practices for addressing cardiovascular disease, stroke, or diabetes, and as a result of collaboration between RTI investigators and local partners, determining approaches for future work. In a couple of cases, the information has pointed the way to target research efforts more narrowly or to build on software programs and modeling to enhance clinical and policy decision making in the countries in question.

In this chapter, we review briefly the pilot projects, recognizing their limitations of time (on average, 18 months in all) and resources. Of the seven studies, three were conducted in India, two in Indonesia, and one each in China and Sri Lanka. The NCDs of interest were stroke, cancer (cervical; oral), diabetes, chronic kidney disease of unknown etiology (CKDu), and obesity and low birth weight. In all cases, we focus on the outcomes of these projects and the conclusions and recommendations that the investigators—from both RTI and local partners—drew from their work.

Many of these suggestions fall into the category of lessons learned. Some are country-specific and some are more generally applicable to LMICs in which these disorders are emerging or posing significant challenges to the health of patient populations and to public health more generally. A few projects

relied on advanced information technologies, the internet, or sophisticated modeling techniques. All addressed issues of critical concern to our in-country collaborators; maximized the advantage of their insights on potentially effective interventions; explored both facilitators for and barriers to successful implementation of prevention, screening, counseling, and treatment initiatives; and thought creatively about next steps.

Review of Project-Specific Accomplishments and Recommendations

In India, projects related to screening for and treatment of patients with oral cancer (Chapter 1) and cervical cancer (Chapter 2) enhanced our understanding of the problems and led to specific recommendations for improving public health and health care to enhance detection and facilitate early treatment. Effective screening and treatment of oral cancer in regional cancer centers are hampered by limited staffing at the centers, increasing use of tobacco products among these populations, and presentation for treatment at later stages of the disease. Important steps to address oral cancer include initiating health policies to regulate and make tobacco products more expensive, educating local healers to increase referrals to cancer centers earlier in the disease, and enhancing systems of care to maximize the effectiveness of existing medical staff. Increased staff resources may also help to improve patient outcomes when coupled with improvement in patient flow.

Also in India, increased efforts at prevention and early diagnosis—such as human papillomavirus (HPV) vaccination for girls and screening and follow-up of women—can enhance cervical cancer detection and treatment. Better evaluation efforts to enhance efficiency and effectiveness in the health care setting have the potential to enhance these programs and activities further.

One pilot project developed and applied a simulated population model to better understand the rapidly increasing prevalence of overweight and obese children and adults in Indonesia and to examine the links between low birth weight in infants, the phenomenon of stunting among children, and obesity in later years (Chapter 3). The project also sought to project future rates of these conditions and estimate the effect on rates of NCDs. The study featured an innovative survey to provide timely data for some of the modeling efforts. Understanding the trajectory of obesity and related diseases will be useful to policy makers in developing public health and health care interventions based on the health and economic costs of those diseases.

Three other pilot projects in three different LMICs entailed brief to complex interventions (one for diabetes, two for stroke). All sought to change behaviors of clinicians or patients (or both) to facilitate use of evidence-based information, prevention strategies, and treatment options. The specific activities differed markedly across these efforts, chiefly in response to the real or perceived needs and concerns of local partners and interest in evaluating innovative interventions.

In a clinical setting in India (Chapter 4), internet-generated patient education handouts about diabetes medications were generated in the local language (Malayalam). These were given to patients, as part of the medical visit, to inform them about diabetes management, enhance patient motivation, and improve diabetes control. Although patients and staff found the handouts useful (and wished they were also available for other conditions), barriers such as unpredictable lapses in internet access complicated the overall implementation.

In China, interfaces between electronic medical systems for stroke care were integrated to automate, at least partially, the collection of data to measure important care processes and outcomes of both treating acute stroke patients and preventing recurrence (Chapter 5). One element of improving stroke care quality is the measurement of key clinical processes, which is usually labor-intensive. Stroke programs in the United States, for example, employ full-time stroke coordinators to facilitate measurement and feedback for key care processes. Reducing the administrative burden of collecting these data, particularly in LMICs, will make measurement and feedback more feasible. Such advances, based on available information technology, will allow hospitals to devote more time to improving processes that are critical components of caring for stroke patients.

A brief intervention in community health centers in Indonesia aimed to enhance patient knowledge of stroke risk factors and provide motivation for change in patient behavior and in the delivery of health care in this small pilot program (Chapter 6). Future efforts to enhance understanding of stroke risk factors will need to include specific training to enhance (yet simplify) workflow, such as incorporating an existing behavioral psychologist to support patients (and families) in making lifestyle changes necessary to reduce the future occurrence of stroke.

Finally, CKDu in Sri Lanka (and other LMICs) (Chapter 7) is an important but not well-understood cause of renal failure. Understanding the problem

better will entail strengthening disease registries and surveillance reporting systems for cases of CKDu and developing capacity in national environmental toxicology and epidemiological networks. This will call for expanding the harmonization of laboratory equipment, protocols, and training to ensure data quality. It also calls for creating an economic evaluation of CKDu to model the costs and societal impact on Sri Lanka as a whole and specific communities in particular. Such efforts, and the resulting information, can provide a basis for advocacy to prevent this condition and improve treatment for patients who are already affected by it.

Products and Next Steps for These RTI Grand Challenge Pilot Projects

These RTI Grand Challenge pilot projects were conducted largely in 2013 and 2014. RTI also convened a one-day summary conference in 2015 where the investigators and outside experts presented and extensively discussed these projects and their outcomes. This symposium prompted us to prepare this book. Many investigators have published meeting abstracts or journal manuscripts,¹⁻⁵ and others are exploring opportunities for grant support through the US National Institutes of Health. Some of the project leads have given presentations or prepared reports for government officials in the host countries.

Equally important, this RTI Grand Challenge gave RTI researchers an opportunity to experience conducting research in LMICs. More important, they were able to begin developing collaborations with researchers and clinicians in these countries. These collaborative networks will likely be the basis of multiple future studies, including some that go well beyond activities planned during the RTI Grand Challenge.

Looking Ahead: Recommendations for Future Research and Related Actions

As a result of the experience gained from this group of seven pilot projects, we and the investigators offer the following recommendations to enhance our collaborative work to reduce the burden of NCDs in LMICs. These reflect the key findings or lessons learned identified specifically in Chapters 1 through 7.

Establish Research Infrastructures That Facilitate Studies in LMICs

Many US-based research organizations and institutions may not be familiar with the procedures and requirements for conducting studies in LMICs. Developing a project management and administrative support system dedicated to LMIC research will likely facilitate such studies and encourage researchers to pursue work in this area. Furthermore, creating and fostering “communities of interest,” bringing together those interested in LMIC-based research with others who have experience in this area, will also help to identify and prospectively address governmental, health care system, and cultural barriers that often impede studies of NCDs in these countries.

Involve Professionals from LMICs

A foundational principle of community-based participatory research is the inclusion of individuals from the communities being studied. Community-based participatory research emphasizes the community’s role in identifying research priorities, developing study plans, reviewing study findings, and disseminating results. These principles clearly extend to collaborative research of the sort documented in this book.

Thus, for research to improve NCD outcomes in LMICs, a critical step will entail involving research and health care professionals in those countries in all aspects of such efforts. This explicitly includes planning studies, implementing the proposed programs, tracking performance, documenting outcomes, and disseminating results. Focusing projects on areas where research collaborators are located and where research infrastructures already exist will also increase the efficiency of work in LMICs.

Provide Flexible Research Opportunities

Many preliminary or proof-of-concept studies to develop or test interventions can be performed quickly with limited budgets. If they prove successful, larger pilot studies can be undertaken. Even if not fully successful, replication or scaled-up efforts, drawing on the specific lessons learned from the pilot, may be possible.

For preliminary studies, developing a cash reserve to provide small amounts of funding quickly would be useful. Flexible approaches to financial support for various types of studies, but particularly to explore potentially promising interventions and to reach out to changing health care environments in LMICs, offer attractive options for expanding this type of research across these (or other) NCDs in these (or other) LMICs.

Develop Improved Data Collection Systems in LMICs

Collecting epidemiologic, medical, and patient-reported data will be vital for developing interventions with the potential to improve NCD outcomes in LMICs; similarly, such capabilities are a prerequisite for assessing the impact of such interventions. This imperative clearly includes data collection in different regions of or among diverse populations in a given country.

Few LMICs have comprehensive data collection systems today. Most have systems that acquire only limited information in specific regions of the country. Fortunately, developing data collection and analysis systems in LMICs is relatively low in cost. In some cases, these efforts can be included as part of broader studies.

In addition to assisting with research, intervention development, and program evaluation, systems to collect vital statistics and other epidemiologic, health care, and patient outcomes information are needed. They can be expected to strengthen existing health care systems, to expand and increase the impact of prevention activities, and, at least indirectly, to improve patient outcomes.

Consider Mutual Benefits from Studies in LMICs

Approaches or strategies developed in LMICs may be of benefit in certain US health care settings. This can be classified as “reverse innovation”; that is, effective and low-cost programs developed in LMICs may also provide effective and low-cost health care benefits advantageous for specific US population groups.

Research costs are often substantially lower in LMICs than in the United States (or other highly developed countries). For that reason, performing work in LMICs that is mutually beneficial may be financially advantageous across the board. In developing future studies, researchers need to think strategically about approaches that are feasible in both LMICs and the United States. Such interventions and study designs might employ mobile technologies, telemedicine, or community health workers. In particular, disruptive innovations that can potentially have substantial benefits in LMICs may also be game-changers in higher-income countries.

Include a Broad Range of Outcomes

Many health care studies conducted in LMICs have focused on changes in mortality rates. Although this is appropriate for studies of infectious diseases

and other potentially fatal acute conditions, it is not the only outcome of interest for studies of NCDs. Studies of interventions to improve NCD outcomes need to include measures such as morbidity and quality of life, with the latter assessed through patient-reported outcomes. Also of interest are measures of the use of services and costs of care. Finally, apart from the focus on patients and their outcomes are concerns with impacts on clinicians and other staff in hospitals, clinics, and other settings, as well as quality of life. These also need to be measured when expanded use of technologies and major changes to settings, workflow, or established procedures are set in motion.

Plan for Translation and Sustainability of Study Findings

In planning for studies of NCDs in LMICs, considering the translation of research findings is critical. Investigators, funders, and policy makers need to think in advance about how study results can be used to produce sustainable actions. These considerations include broader implementation of successful interventions (scaling them up) and support for policies that facilitate and enhance such interventions. Part of conducting ethical and responsible research in LMICs is planning for a continued benefit of a study to the relevant populations after the research is completed.

Concluding Thoughts

The epidemic of NCDs represents a challenge to the health and well-being of the world's population. The disproportionate impact in LMICs is particularly challenging because they have many fewer resources to quell the epidemic. Clearly, acute treatment is not a viable sole option in this fight. As some have said, you cannot treat yourself out of the epidemic of, for instance, cardiovascular disease.

Numerous important initiatives can be considered. For example, population health approaches can reduce the development of risk factors (or exposures to environmental risk factors). Public policy initiatives can reduce tobacco use, improve the availability of nutritious food, increase the number of safe areas for physical activity, and reduce time spent in front of electronic screens. Modeling studies can provide detailed information about options that public health officials can use to make important decisions about the focus of proposed programs in the context of estimated costs and outcomes over the long term. In the health care system, a shift from on-demand acute care to preventive care provided by nonphysician professionals skilled in behavior

change, together with use of contemporary information technologies for patient and family education, all offer opportunities for both primary and secondary prevention efforts.

As the RTI Grand Challenge projects demonstrate, creative use of expertise and local partnerships can provide an approach that is more cost-effective and culturally sensitive to the populations to be served and the systems to be enhanced. One very important lesson is that partnerships with local experts in LMICs—who have a clear understanding of cultural, economic, and systems factors—are an invaluable ingredient in addressing the expanding and devastating problem of NCDs. These relationships will be critical in future work to reduce the impact of NCDs on the world's populations. In pursuing these goals, RTI has been honored and gratified to be able to pursue its mission of improving the human condition. We look forward to contributing to this important enterprise in coming years.

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Contributors

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This book succinctly summarizes the results of a Grand Challenge project from RTI International. If you are looking for a work long on hand-wringing about the challenges of noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs), this is not for you.

But if you are searching for a series of creative, inspiring, and yet practical approaches that target significant problems for humanity, transcend traditional segmented disciplines, are challenging to implement, but are clearly achievable . . . this book is just what the doctor ordered!

—Gray Ellrodt, MD, Chief of Medicine and Director of the Internal Medicine Training Program,
Berkshire Medical Center

The alarm has been sounded. Developing countries are facing major public health challenges with the rapid rise of noncommunicable diseases. Although hidden behind the news headlines and a clearly important focus on the suffering caused by the Ebola and Zika viruses, the alarming and rapid increase in the incidence of chronic diseases in low- and middle-income countries (LMICs) must be addressed by the global health community. This clarion call was highlighted by the United Nations, particularly in its statement that members must ensure healthy lives and promote well-being and, specifically, “by 2030 reduce by one third premature mortality from non-communicable diseases through prevention and treatment.”

RTI International has responded to this evolving crisis by applying its considerable expertise across a range of interventions in several LMICs. The featured pilot projects, launched under a “Grand Challenge” framework, are grounded in the real world of primary health care. They were implemented in collaboration with frontline health care professionals who are grappling with this surge in largely preventable diseases. Effective partnerships will be crucial for meeting the global challenge, and RTI has offered a bold but pragmatic roadmap for future engagement with local practitioners, aimed at addressing this new global health threat and saving lives.

—Aaron Williams, Director of the US Peace Corps (2009–2012),
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