

Figure 2: Main reasons for dissatisfaction of Japanese population with the health-care system

A public opinion survey on health-care policy was done in January, 2010, by Japanese experts.⁵⁰ Two-stage cluster sampling of 1650 individuals (aged ≥ 20 years) was used to gather information about public opinion on various aspects of health-care policy. The overall response rate was 62%. When compared with a survey in 2006 with the same set of questions, the results of the recent survey suggest that over the past few years, public dissatisfaction with the decision-making process of the health-care system has increased, while public satisfaction with the medical services and treatments has increased.

issues about quality, access, or costs, but the lack of fairness and public participation in decision making (figure 2).⁵⁰ Behind this lack of fairness and public participation in decision making is the lack of appropriate use of evidence. Decision making—whether local, national, or global—will always remain political, but it can still be informed by better science and evidence to frame key choices, especially approaches that take into account the overall context.

Although a general social agreement exists about the need for structural reform, no one is willing to take the political risk to break the policy inertia and transform the health system. The system's inefficiencies could be tolerated in Japan's period of high economic growth, but not in today's climate of economic stagnation. We believe that a bold alliance of stakeholders across political parties and positions, beyond the vested interests of individual groups, is needed to stimulate structural reform of Japan's health system.

Second, redefine the role of central and local governments. The notion of human security requires both top-down and bottom-up approaches to reform Japan's health system. From the top-down perspective, Japan needs central policies that give more emphasis to people-centred health interactions by breaking down the ministerial silos of authority and responsibility. The greatest barrier to reform is Japan's antiquated and entrenched institutional mechanisms for health-policy making that provide few opportunities for domestic and global health experts to interact. Towards the goal of providing independent and robust analyses of both domestic and global health policies, Japan needs to establish agencies such as the Centers for Disease Control and Prevention, National Institutes of Health, and Institute of Medicine in the USA, and National Institute of Clinical Excellence and Public Health in the UK. At the

same time, from the bottom-up perspective, Japan needs to empower regional and community planning entities that can expand autonomy for the regions. Design and implementation of these changes will require new kinds of dialogue and decision making among groups that have not previously collaborated, including the medical association, government organisation, private industry, and civil society groups.

Japan's health policy is decided uniformly by the central government and with little discretion from the local governments. Therefore, at the local level, prefectural governments should serve as the key organisations for citizens to participate in forming and implementing health policy. The first step would be the election of politicians who are committed to managing and sustaining the regional health-care system. The consolidation of the social insurance plans at the prefectural level would not only improve fairness of each organisation's financial contribution, but also enhance the authority of the prefectural governors. Their mandate would be to exercise tighter control over provision of care to improve efficiency in the allocation of health-care resources and their functions in the region. Providers' performance must be monitored, and hospitals and clinics should be consolidated to improve efficiency.

The triple disasters—earthquake, tsunami, and nuclear crisis—that Japan is now confronting in the Tohoku area have created the nation's worst humanitarian crisis since World War 2. Remote villages along the coast hit by the tsunami are among the regions with the fastest ageing populations in Japan. The prevalence of hypertension and diabetes is high among survivors, and there is a chronic shortage of health workforce and little access to quality care.⁵¹ In these areas, the major issues for the Japanese health system—ie, ageing population, chronic disease, little access to quality services, and lack of a health workforce—have been magnified after the disaster. This confluence of crises represents one possible future scenario for all Japan. Thus, reconstruction of the health system in the Tohoku area represents a test case for future reform of the Japanese health system. We believe that rebuilding the health system in Tohoku provides an opportunity for a positive reform of the Japanese health-care system based on the notion of human security.

Third, improve the quality of health care. Japan lacks systematic measures and incentives to improve quality.⁵² The accreditation system of subspecialties is not well established—physicians are free to proclaim and practice any specialty they desire, and national quotas for training subspecialists based on the expected need, and the resources for meeting the required level of experience do not exist.¹⁷ Although the subspecialties are under the general organisation of the Japanese Board of Medical Specialties,⁵³ the board does not have the authority to set quotas or standardise accreditation requirements. Subspecialty organisations should start by setting such quotas and building clinical databases, such as those that

have been developed by the Japanese Society of Thoracic Surgery and other subspecialties.⁵⁴

The lack of quotas has led to the training of too many subspecialists. Only a small proportion continue and choose a career in their subspecialties and the rest shift to general practice without formal training as family doctors. General practice is not established as a subspecialty because few medical schools in Japan have a department of primary care or general practice. It is the underlying reason why continuity and comprehensiveness of primary care remains poor in the Japanese health system.¹¹ To address this mismatch in training and practice for physicians, Japan requires a long-range reform of medical education,^{55,56} which could include a retraining programme for general practice for subspecialty physicians as a postgraduate educational system in medical schools. This programme should emphasise skills in communication with patients, management of team practice, and coordination of local health-care resources to improve accountability for local health outcomes.

To effectively allocate subspecialty physicians and other resources, a regional planning committee composed of providers, local government, and citizens should be organised. The quality of hospital performance should also be monitored through mandatory reports that are automatically downloadable from a national hospital information system. This monitoring would enhance quality through peer competition. The reporting system for hospitals participating in the case-mix prepayment system already provides the basis for creating an effective hospital monitoring system.⁵⁷ Small hospitals mainly providing chronic care should be further encouraged to become skilled nursing facilities or cared housing units.

Once professional and hospital organisations have shown the public that they have committed themselves to improve quality and shown their willingness to make their efforts transparent, they would be in a better position to demand increased resources for health care. This demand would be an issue at the national and prefectural levels.

Fourth, commit to global health. The key strategic agenda for Japan is to reconsider the meaning of global health in ageing populations and to identify areas in which Japan has greater expertise. This *Lancet* Series has showcased the wealth of knowledge and expertise for health and health systems, especially related to universal coverage, that Japan has accumulated in the past 50 years in its quest to improve the health and wellbeing of its people. The Japanese experiences and expertise are highly relevant in an era of scaling up interventions to achieve the health-related Millennium Development Goals (MDGs). Additionally, Japan's experience and knowledge related to health insurance and long-term care^{10,17,20} will be huge assets in the post-MDG movement of global health towards universal coverage and long-term care in ageing societies.^{2,18} These assets should be used by expanding and deepening Japan's financial and

substantive commitments through overseas development assistance. That is, not cut back, despite the pressing demands for reconstruction after the disaster.

Conclusions

Can we do all the tasks presented in these four reforms? Our belief is that Japan must and can. Our four reforms are not independent. Indeed they must be done simultaneously. Human security would be the unifying theme to reform the structure of the central and local governments. Once the responsibilities of the central and local governments are more clearly defined, with more evidence of professional accountability made available, then the public would be more willing to allocate additional resources to health care. To enable this transformation, we have advocated the consolidation of plans for social health insurance at the prefectural level so that their premiums could be linked more directly to the delivery system.¹⁰ When the first three goals are achieved, Japan would be in an improved position to expand its commitment to global health.

The need for change has become more urgent after the disaster of March, 2011. Our recommendations must be adopted now and implemented in 3–5 years. This time is not just for reform but also for rebirth. The issues have become too critical to rely on incremental adjustments that have characterised Japanese policy making. We should take note that Japan's past calamities have often been followed by major changes.²⁸ After the Great Kanto Earthquake of 1923, Japan turned to militarism. After defeat in World War 2, and the dropping of the atomic bombs by the USA, Japan adopted a pacifist constitution in 1947 and achieved peaceful growth. After the Great Hanshin-Awaji (Kobe) Earthquake in 1995, Japan turned inward forcefully. Similarly, Japan's recent catastrophe could have a huge effect on the nation's future.²⁸ We believe those forces of change must be channelled in a positive direction.

Already, the signs are promising. In response to the crisis, Japan has had an outpouring of passionate young people who are committed to helping those devastated by the disasters. Using innovative social media, they have gathered and diffused information, garnered support for projects, and launched massive donation campaigns.⁵⁸ The Japanese version of a new public movement is underway, led by agents for innovative change, hoping to move the system from centralised decision making to a more decentralised people-oriented approach. The crisis has also shown that Japan still shares a strong sense of social cohesion, trust, and reciprocity. Human security approaches to disaster relief and health-care provision for all can be the foundation of Japan and the world in the 21st century.

During this difficult period, Japan has received generous support from all over the world. The time now is for Japan to give back to the global community. We propose that Japan should act as a platform for research

and development of health systems and innovations, drawing lessons from all over the world about universal coverage, equity and healthy ageing in the context of human security, humanitarian responses to disasters, and health effects of radiation exposure. We believe this *Lancet* Series initiates a new era in which these hurdles can be overcome, and that broader lessons can be learned from Japan's successes and problems of the past 50 years.

Contributors

KS, MRR, HH, and NI set the conceptual framework for the report, and KS, HH, AN, and TT did the literature search. KS, HH, NI, and MRR contributed to writing the report. AN, TT, HM, KT, and MRR contributed to the critical revision. All authors contributed to the discussion and have seen and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This work is partly funded by the generous support from the Bill & Melinda Gates Foundation and the China Medical Board and a research grant from the Ministry of Health, Labour and Welfare (H23-seisaku-shitei-033). We thank Tomoko Suzuki and Tadashi Yamamoto for their administrative support. The views expressed in this report are solely those of the authors.

References

- Reich MR, Ikegami N, Shibuya K, Takemi K. Fifty years of pursuing a healthy society in Japan: achievements and challenges. *Lancet* 2011; published online Sept 1. DOI:10.1016/S0140-6736(11)60274-2.
- Latko B, Temporão JG, Frenk J, et al. The growing movement for universal health coverage. *Lancet* 2011; 377: 2161–63.
- Garrett L, Chowdhury AMR, Pablos-Méndez A. All for universal health coverage. *Lancet* 2009; 374: 1294–99.
- WHO. Sustainable health financing, universal coverage and social health insurance. World Health Assembly Resolution 58.33. May, 2005. http://www.who.int/health_financing/documents/cov-wharesolution5833/en/index.html (accessed July 20, 2011).
- McIntyre D, Garshong B, Mtei G, et al. Beyond fragmentation and towards universal coverage: insights from Ghana, South Africa and the United Republic of Tanzania. *Bull World Health Organ* 2008; 86: 871–76.
- Agyepong IA, Adjei S. Public social policy development and implementation: a case study of the Ghana National Health Insurance scheme. *Health Policy Plan* 2008; 23: 150–60.
- Twahirwa A. Sharing the burden of sickness: mutual health insurance in Rwanda. *Bull World Health Organ* 2008; 86: 823–24.
- Halstead SB, Walsh JA, Warren KS, eds. Good health at low cost. New York, NY: Rockefeller Foundation, 1985.
- Carrin G, Mathauer I, Xu K, Evans DB. Universal coverage of health services: tailoring its implementation. *Bull World Health Organ* 2008; 86: 857–63.
- Ikegami N, Yoo B-K, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges *Lancet* 2011; published online Sept 1. DOI:10.1016/S0140-6736(11)60828-3.
- The Lancet. Japan: health after the earthquake. *Lancet* 2011; 377: 968.
- Ide S, Baltay A, Beroza GC. Shallow dynamic overshoot and energetic deep rupture in the 2011 Mw 9.0 Tohoku-Oki Earthquake. *Science* 2011; 332: 1426–29.
- National Police Agency. Cause of death in the Great East Japan Earthquake, 2011. <http://www.npa.go.jp/archive/keibi/biki/index.htm> (accessed May 29, 2011).
- Tokyo Electric Power Company. Analysis and impact assessment on Fukushima Daiichi nuclear disaster. 2011. <http://www.tepco.co.jp/nu/fukushima-np/index-j.html#anchor02> (accessed May 29, 2011).
- McCurry J. Japan: the aftermath. *Lancet* 2011; 377: 1061–62.
- Fukukawa K, Arai H. Earthquake in Japan. *Lancet* 2011; 377: 1652.
- Hashimoto H, Ikegami N, Shibuya K, et al. Cost containment and quality of care in Japan: is there a trade-off? *Lancet* 2011; published online Sep 1. DOI:10.1016/S0140-6736(11)60987-2.
- Llano R, Kanamori S, Kunii O, et al. Re-invigorating Japan's commitment to global health: challenges and opportunities. *Lancet* 2011.
- Ikegami N, Saito E, Kondo N, et al. What has made the population of Japan healthy? *Lancet* 2011; published online Sept 1. DOI:10.1016/S0140-6736(11)61055-6.
- Tamiya N, Noguchi H, Nishi A, et al. Population ageing and wellbeing: lessons from Japan's long-term care insurance policy *Lancet* 2011; published online Sept 1. DOI:10.1016/S0140-6736(11)61176-8.
- London School of Hygiene and Tropical Medicine. 'Good health at low cost' 25 years on. What makes a successful health system? London: London School of Hygiene and Tropical Medicine. 2011. <http://healthsystems.lshtm.ac.uk/ghlcmontreuxflyer.pdf> (accessed July 23, 2011).
- Ministry of Health Labour and Welfare. Shugyo keitai no tayouka ni kansuru sougou jittai chousa. Comprehensive survey on diversified working conditions. 2003. (in Japanese). <http://www.mhlw.go.jp/toukei/itiran/roudou/koyou/keitai/03/kekka4.html> (accessed May 29, 2011).
- Roberts MJ, Hsiao W, Berman P, Reich MR. Getting health reform right: a guide to improving performance and equity. London: Oxford University Press, 2004.
- Hashimoto S, Kawado M, Seko R, et al. Trends in disability-free life expectancy in Japan, 1995–2004. *J Epidemiol* 2010; 20: 308–12.
- Ikegami N, Campbell JC. Japan's health care system: containing costs and attempting reform. *Health Aff (Millwood)* 2004; 23: 26–36.
- Ministry of Finance. Heisei 21 nendo ippan kaikei saishutu yosan. Annual expenditure plan from general account 2009. (in Japanese). Tokyo: Ministry of Finance, 2009.
- OECD. Economic Outlook 2010. Paris: Organisation for Economic Co-operation and Development, 2011.
- The Economist. The fallout. March 17, 2011. <http://www.economist.com/node/18395981> (accessed July 23, 2011).
- Onishi N, Fackler M. In nuclear crisis, crippling mistrust. http://www.nytimes.com/2011/06/13/world/asia/13japan.html?pagewanted=1&_r=1&sq=fukushima&st=cse&scp=3 (accessed July 1, 2011).
- Honda H. Nuclear energy politics in Japan (2)—coalition formation and conflict management. *Hokkaido Law Rev* 2003; 54: 205–62.
- Ablin RJ. Japanese HIV-blood trial. *Lancet* 2002; 359: 446.
- Yasunaga H. Risk of authoritarianism: fibrinogen-transmitted hepatitis C in Japan. *Lancet* 2007; 370: 2063–67.
- Association of the British Pharmaceutical Industry: Pharmaceutical Industry Competitiveness Task Force. Competitiveness and performance indicators 2005. 2006. www.advisorybodies.doh.gov.uk/pictf/2005indicators.pdf (accessed May 25, 2011).
- Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. *Health Econ* 2005; 14: 269–92.
- Hirai Y, Kinoshita H, Kusama M, Yasuda K, Sugiyama Y, Ono S. Delays in new drug applications in Japan and industrial R&D strategies. *Clin Pharmacol Ther* 2010; 87: 212–18.
- Kyo S, Takamoto S. Ventricular assist device. *Kyobu Geka* 2009; 62 (8 suppl): 704–11.
- Murashige N, Matsumura T, Kami M. Disseminating Japan's immunisation policy to the world. *Lancet* 2011; 377: 299.
- Ministry of Health, Labour and Welfare. Polio vaccine working team report for the Health Sciences Council of the Ministry of Health, Labour and Welfare (polio vaccine sagyo team houkokusho). 2011. (in Japanese). <http://www.mhlw.go.jp/stf/shingi/2r98520000014wdd-att/2r98520000016rr8.pdf> (accessed May 29, 2011).
- Ministry of Health, Labour and Welfare. Advisory panel report on vaccine implementation evaluation for the Health Sciences Council of the Ministry of Health, Labour and Welfare (Vaccine hyoka ni kansuru shoiinkai houkokusho). 2011. (in Japanese). <http://www.mhlw.go.jp/stf/shingi/2r98520000014w74-att/2r98520000014w9e.pdf> (accessed May 29, 2011).
- Cyranoski D. A healthier Japan. *Nature* 2011; 474: 136.
- Government of Japan. Life innovation: a society of health and longevity. Highlighting Japan. Tokyo: Public Relations Office, Government of Japan, 2010.

- 42 Miyazawa K, ed. Iryo to fukushi no sangyo renkan. Inter-industrial input output analysis of health care and welfare services. Tokyo: Toyokeizai-shinpo, 1992 (in Japanese).
- 43 Miyazawa K, ed. Iryo to fukushi no sangyo-renkan ni kansuru bunseki kenkyu hokokusho. Inter-industrial input-output analysis on healthcare and welfare service. Research report funded by Ministry of Health Labour and Welfare. Tokyo: Institute of Health Economics and Policy, 2003. (in Japanese). www.ihep.jp/demo/member/03104.pdf (accessed July 20, 2011).
- 44 Ide H, Yasunaga H, Kodama T, Koike S, Taketani Y, Imamura T. The dynamics of obstetricians and gynaecologists in Japan: a retrospective cohort model using the nationwide survey of physicians data. *J Obstet Gynaecol Res* 2009; 35: 761–66.
- 45 Ide H, Yasunaga H, Koike S, Kodama T, Igarashi T, Imamura T. Shortage of pediatricians in Japan: a longitudinal analysis using physicians' survey data. *Pediatr Int* 2009; 51: 645–49.
- 46 WHO. The World Health Report 2000. Geneva, Switzerland: World Health Organization, 2000: 1–215.
- 47 Ministry of Health Labour and Welfare. Heisei 20 nen juryo kodou chosa. Survey of patient behavior 2008. 2009. (in Japanese).
- 48 Ding H, Koinuma N, Ito M, Nakamura T. Strategies for improving pediatric services in Japan. *Tohoku J Exp Med* 2005; 206: 195–202.
- 49 Commission on Human Security. Human security now. In: Ogaka S, Sen A, eds. Commission on Human Security: New York, NY, 2003.
- 50 Health and Global Policy Institute, Japan. Summary of the 2010 public survey on healthcare in Japan. 2010 http://www.hgpi.org/handout/2010-02-15_25_787459.pdf (accessed May 25, 2011).
- 51 Yomiuri Shimbun. Two patients on hemo-dialysis dead at evacuation center. 2011. (in Japanese). <http://www.yomiuri.co.jp/national/news/20110402-OYTIT00309.htm> (accessed May 25, 2011).
- 52 Henke N, Kadonaga S, Kanzler L. Improving Japan's health care system. http://www.mckinseyquarterly.com/Improving_Japans_health_care_system_2311 (accessed July 23, 2011).
- 53 Nihon senmonisei hyoka nintei kikou. Japanese Board of Medical Specialties. (in Japanese). <http://www.japan-senmon-i.jp> (accessed May 29, 2011).
- 54 National Clinical Database. 2011. <http://www.ncd.or.jp> (accessed July 20, 2011).
- 55 Chen FM, Burstin H, Huntington J. The importance of clinical outcomes in medical education research. *Med Educ* 2005; 39: 350–51.
- 56 Chen FM, Phillips RL Jr, Schneeweiss R, et al. Accounting for graduate medical education funding in family practice training. *Fam Med* 2002; 34: 663–68.
- 57 National Hospital Organization. Clinical indicator. 2009. <http://www.hosp.go.jp/7,7015.html> (accessed July 20, 2011).
- 58 Sato N, Yamazaki M. How generation next is rebuilding Japan. http://blogs.hbr.org/cs/2011/05/how_generation_next_is_rebuild.html (accessed May 28, 2011). Harvard Business Review, 2011.

Adult Mortality Attributable to Preventable Risk Factors for Non-Communicable Diseases and Injuries in Japan: A Comparative Risk Assessment

Nayu Ikeda^{1*}, Manami Inoue², Hiroyasu Iso³, Shunya Ikeda⁴, Toshihiko Satoh⁵, Mitsuhiko Noda⁶, Tetsuya Mizoue⁷, Hironori Imano³, Eiko Saito¹, Kota Katanoda⁸, Tomotaka Sobue⁸, Shoichiro Tsugane², Mohsen Naghavi⁹, Majid Ezzati¹⁰, Kenji Shibuya¹

1 Department of Global Health Policy, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, **2** Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, **3** Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, **4** International University of Health and Welfare Graduate School, Tokyo, Japan, **5** Kitasato Clinical Research Center, Kitasato University School of Medicine, Sagami, Japan, **6** Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo, Japan, **7** Department of Epidemiology and International Health, National Center for Global Health and Medicine, Tokyo, Japan, **8** Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan, **9** Institute for Health Metrics and Evaluation, University of Washington, Seattle, Washington, United States of America, **10** MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

Abstract

Background: The population of Japan has achieved the longest life expectancy in the world. To further improve population health, consistent and comparative evidence on mortality attributable to preventable risk factors is necessary for setting priorities for health policies and programs. Although several past studies have quantified the impact of individual risk factors in Japan, to our knowledge no study has assessed and compared the effects of multiple modifiable risk factors for non-communicable diseases and injuries using a standard framework. We estimated the effects of 16 risk factors on cause-specific deaths and life expectancy in Japan.

Methods and Findings: We obtained data on risk factor exposures from the National Health and Nutrition Survey and epidemiological studies, data on the number of cause-specific deaths from vital records adjusted for ill-defined codes, and data on relative risks from epidemiological studies and meta-analyses. We applied a comparative risk assessment framework to estimate effects of excess risks on deaths and life expectancy at age 40 y. In 2007, tobacco smoking and high blood pressure accounted for 129,000 deaths (95% CI: 115,000–154,000) and 104,000 deaths (95% CI: 86,000–119,000), respectively, followed by physical inactivity (52,000 deaths, 95% CI: 47,000–58,000), high blood glucose (34,000 deaths, 95% CI: 26,000–43,000), high dietary salt intake (34,000 deaths, 95% CI: 27,000–39,000), and alcohol use (31,000 deaths, 95% CI: 28,000–35,000). In recent decades, cancer mortality attributable to tobacco smoking has increased in the elderly, while stroke mortality attributable to high blood pressure has declined. Life expectancy at age 40 y in 2007 would have been extended by 1.4 y for both sexes (men, 95% CI: 1.3–1.6; women, 95% CI: 1.2–1.7) if exposures to multiple cardiovascular risk factors had been reduced to their optimal levels as determined by a theoretical-minimum-risk exposure distribution.

Conclusions: Tobacco smoking and high blood pressure are the two major risk factors for adult mortality from non-communicable diseases and injuries in Japan. There is a large potential population health gain if multiple risk factors are jointly controlled.

Please see later in the article for the Editors' Summary.

Citation: Ikeda N, Inoue M, Iso H, Ikeda S, Satoh T, et al. (2012) Adult Mortality Attributable to Preventable Risk Factors for Non-Communicable Diseases and Injuries in Japan: A Comparative Risk Assessment. PLoS Med 9(1): e1001160. doi:10.1371/journal.pmed.1001160

Academic Editor: Peter Byass, Umeå Centre for Global Health Research, Sweden

Received: July 28, 2011; **Accepted:** December 6, 2011; **Published:** January 24, 2012

Copyright: © 2012 Ikeda et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare (H22-seisaku-shitei-033) and a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science (No. 2239013). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: CI, confidence interval; HTLV-1, human T-lymphotropic virus type 1; LDL, low density lipoprotein; NHNS, National Health and Nutrition Survey

* E-mail: ikedan@m.u-tokyo.ac.jp

Introduction

Controlling risk factors for non-communicable diseases and external causes is essential for the improvement of adult health. Chronic diseases and injuries are the leading causes of global mortality, accounting for 63% and 9%, respectively, of 57 million deaths in 2008 [1]. The five major risk factors for deaths in the world are high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity, which contribute to non-communicable diseases and are modifiable with effective interventions [2]. In such an environment, informed decision-making on priority setting for health policies and programs needs consistent and comparative evidence about how many deaths would be averted by changing profiles of preventable risk factors in a population.

The population of Japan has the longest life expectancy at birth in the world. Life expectancy at birth for Japanese women was 54.0 y in 1947 and rapidly increased until 1986, at which point, at 81.0 y, it became the longest in the world for the first time; female life expectancy at birth also reached its highest ever worldwide figure, 86.4 y, in Japan in 2009 [3]. The continuous extension of longevity was largely explained by a decline in the rate of mortality for communicable diseases among children and young adults during the 1950s and the early 1960s and for stroke since the late 1960s [4]. Current leading causes of death are malignant neoplasm, heart disease, and cerebrovascular disease, accounting for more than 50% of total deaths in 2009 [5]. Accidental injuries and suicide have also ranked in the top ten causes of death for the past 50 y [5], and particularly suicide in the working population is a serious social problem reflecting the prolonged economic recession since the 1990s [4]. To further enhance the health status of the Japanese population, it is therefore crucial to prevent deaths from these major causes.

With the aim of increasing the nation's health through the prevention of premature deaths from lifestyle-related diseases, the Japanese government initiated a 10-y national health promotion campaign called Health Japan 21 in 2000 [6]. In this campaign, 59 indicators were established to monitor and improve the management of risk factors and diseases such as diet, smoking, and diabetes. However, the performance of Health Japan 21 was not necessarily satisfactory: there was progress on 60% of the 59 indicators, including decreasing daily salt intake, while deterioration or no improvement was observed for the remaining 40%, for example, the prevalence of overweight and obesity decreased in women aged 40–60 y but increased in men aged 20–60 y [7]. Success of national health promotion campaigns may partly depend on whether the stewardship of central and local governments exists for coordinating diverse activities and investing resources in priority areas with reference to scientific evidence on the disease burden attributable to modifiable risk factors. Although a number of past studies have quantified population-attributable fractions or impacts on life expectancy for individual risk factors in Japan [8–16], no study to our knowledge has used a single comprehensive framework to assess and compare these impacts across multiple risk factors.

In the present study, we therefore aimed to provide the most comprehensive and comparative assessment of preventable risk factors for mortality from non-communicable diseases and injuries in the Japanese adult population. We employed a comparative risk assessment strategy to quantify contributions of health risks to disease outcomes [17,18]. This standard systematic approach has already been applied to examine the burden of disease and injury across major risk factors in a few other countries [19–22]. Using

national data sources on risk exposures and cause-specific mortality, as well as epidemiologic evidence on their causal association from large-scale prospective studies and meta-analyses in Japan, this analysis identifies the most important risk factors for deaths and life expectancy at the population level; the results could inform policymakers of which risk factors need to be prioritized in formulating and revising health policies and programs.

Methods

We estimated the number of deaths that would have been saved in 2007 if multiple risk factors had been controlled at their optimal levels as determined by a theoretical-minimum-risk exposure distribution. To quantify and compare the mortality attributable to excess health risks, we used comparative risk assessment methods that have been described in detail elsewhere [18,20]. To summarize, we first calculated the population-attributable fraction of cause-specific mortality for each risk factor, which measures a proportional reduction in mortality that would be achieved if risk factor exposures of a population shifted to an alternative counterfactual distribution that is more favorable. We used the following formula to calculate population-attributable fractions for continuous exposure variables:

Population – attributable fraction =

$$\frac{\int_x RR(x)P(x)dx - \int_x RR(x)P'(x)dx}{\int_x RR(x)P(x)dx}, \quad (1)$$

where $P(x)$ and $P'(x)$ are actual and counterfactual distributions of exposure in the population, respectively, and $RR(x)$ is the relative risk of mortality at exposure level x . The first and second terms in the numerator of this equation represent the total risk of mortality weighted by exposures in the population under current and counterfactual distributions, respectively. This approach allowed us to compute effects of all nonoptimal exposures of individuals for all risk factors in a consistent and comparable way [21]. For risks measured in multiple categories, we used the following generalized formula to calculate population-attributable fractions:

$$\text{Population – attributable fraction} = \frac{\sum_{i=1}^n P_i(RR_i - 1)}{\sum_{i=1}^n P_i(RR_i - 1) + 1}, \quad (2)$$

where i signifies the level of individual categories ($i = 1, \dots, n$).

We then multiplied the number of cause-specific deaths by population-attributable fractions to estimate mortality from diseases (causes of death) associated with each risk factor. The number of deaths attributable to a single risk factor was summed across different causes to obtain the total number of deaths attributable to that risk factor. The number of deaths from a single cause, however, could not be added across risk factors, because they may be causally related and we did not account for such relationships in the estimation of population-attributable fractions of individual risk factors.

We conducted all analyses separately by sex, using Stata version 11 (StataCorp). We restricted analyses to individuals aged 30 y and over, because the number of deaths from non-communicable

diseases is small for younger ages. However, we included those aged 20 to 29 y when estimating deaths from external causes attributable to alcohol use, because the burden was assumed to be substantial in this age group.

Mortality Data

We obtained data on the number of cause-specific deaths in 2007 from vital records [23]. We applied algorithms developed for the Global Burden of Disease 2010 Study to redistribute ill-defined codes (e.g., cardiac arrest, heart failure, and senility) on death certificates that were not supposed to be underlying causes of death [24,25]. This method enabled us to obtain valid, reliable, and comparable data on cause-specific mortality by ensuring consistency and resolving changes across revisions of the *International Statistical Classification of Diseases and Related Health Problems*.

Selection of Risk Factors and Diseases

We included 16 risk factors in this analysis (Table 1). In the selection of risk factors paired with their relevant diseases or injuries, we employed the criteria of a previous study: (i) an availability of evidence on causality or association from high-quality epidemiological studies, (ii) an existence of interventions to modify exposures, and (iii) an availability of data on risk exposures from nationally representative surveys or large population studies [20]. We also included infection by several agents—hepatitis B virus, hepatitis C virus, the bacterium *Helicobacter pylori*, human papillomavirus, and human T-lymphotropic virus type 1 (HTLV-

1)—because they are important risk factors for cancer deaths in Japan [26,27].

Measures and Data Sources of Risk Factor Exposures

Table 2 lists measurements and data sources for the risk factor exposures used in this analysis, and Table 3 shows their basic statistics by sex and age group in 2007. With the exception of tobacco smoking, infections, and alcohol use related to deaths from traffic road accidents, we used individual records from the National Health and Nutrition Survey (NHNS) in 2007. NHNS was a survey based on a nationally representative probabilistic sample to provide data on the health and nutritional status of the Japanese population. This survey included an in-person interview on medication use and lifestyle-related risk factors, a physical examination by health care professionals, and self-administered questionnaires on diet and lifestyle [28].

We used self-reports to quantify exposures to physical inactivity and alcohol use, while we used measured data for other risk factors. In the physical examination for the 2007 NHNS, a blood test was intended to be conducted more than 4 h after a meal, although a number of blood samples were actually drawn less than 4 h after a meal. Because fasting plasma glucose was the unit for relative risk for high blood glucose adopted in the present study, we applied the following conversion equation proposed by the Committee of the Japan Diabetes Society [29,30] to predict equivalents of fasting plasma glucose from measurements of hemoglobin A1c:

Table 1. Risk factors and disease outcomes included in the study.

Risk Factor	Disease Outcomes
High blood glucose	IHD, stroke, diabetes mellitus
High LDL cholesterol	IHD, ischemic stroke
High blood pressure	IHD, stroke, hypertensive diseases, other cardiovascular diseases ^a
Overweight/obesity	IHD; ischemic stroke; hypertensive disease; postmenopausal breast, colon, corpus uteri, kidney, and pancreatic cancers; diabetes mellitus
Alcohol use	IHD; ischemic stroke; hemorrhagic stroke; hypertensive diseases; cardiac arrhythmias; cancers of breast, colorectal, esophagus, mouth, liver, larynx, pharynx, and selected other sites ^b ; diabetes mellitus; liver cirrhosis; acute and chronic pancreatitis; road traffic injuries; falls; homicide and suicide; other injuries
Tobacco smoking	IHD; stroke; aortic aneurysms and dissection; diabetes mellitus; lung, esophagus, mouth, pharynx, stomach, liver, pancreas, cervix, bladder, kidney, and other urinary cancers; leukemia; chronic obstructive pulmonary disease; lower respiratory tract infections; asthma; tuberculosis
Physical inactivity	IHD, ischemic stroke, breast and colon cancers, diabetes mellitus
High dietary trans fatty acids	IHD
Low dietary polyunsaturated fatty acids	IHD
High dietary salt	IHD, stroke, hypertensive disease, other cardiovascular diseases ^a , stomach cancer
Low intake of fruit and vegetables	IHD; ischemic stroke; colorectal, esophagus, lung, mouth, pharynx, and stomach cancers
Hepatitis B virus	Liver cancer
Hepatitis C virus	Liver cancer
<i>H. pylori</i>	Stomach cancer
Human papillomavirus	Cervix uteri cancer
HTLV-1	Adult T-cell lymphoma/leukemia

^aThis category includes rheumatic heart disease, endocarditis, cardiomyopathy, aortic aneurysms, peripheral vascular disorders, and other ill-defined cardiovascular diseases.

^bThis category includes *International Statistical Classification of Diseases and Related Health Problems, 10th edition* (ICD-10) codes D00–D24 (except D09.9), D26–D37 (except D37.9), and D38–D48 (except D38.6, D39.9, D40.9, D41.9, and D48.9).

IHD, ischemic heart disease.

doi:10.1371/journal.pmed.1001160.t001

Table 2. Measurements, data sources, and alternative distributions of risk exposures.

Risk Factor, Exposure Metric, Data Source ^a	Optimal	Guidelines/National Goals
High blood glucose		
Fasting plasma glucose (mmol/l)	4.9 (0.3)	5.6 (0.3) [66]
High LDL cholesterol		
LDL cholesterol (mmol/l)	2.0 (0.4)	3.1 (0.7) [54]
High blood pressure		
Systolic blood pressure (mm Hg)	115 (6)	130 (7) [53]
Overweight/obesity		
Body mass index (kg/m ²)	21 (1)	22 (1) [67]
Alcohol use		
Current alcohol consumption volumes and patterns	No alcohol use ^b	
Alcohol-related road traffic accidents, national road accident data, 2004 [40]	No alcohol use	
Tobacco smoking		
Smoking impact ratio, vital statistics 2007 data [23–25], pooled cohort studies [15,35,36]	No smoking	
Physical inactivity		
Intensity of physical activity	Highly active	
High dietary trans fatty acids		
Percent of total calories from dietary trans fatty acids	0.5 (0.05)	
Low dietary polyunsaturated fatty acids		
Percent of total calories from dietary polyunsaturated fatty acids	10 (1)	
High dietary salt		
Dietary sodium adjusted for total calories (g/d)	0.5 (0.05)	10 (1) [7]
Low intake of fruit and vegetables		
Dietary fruit and vegetable intake adjusted for total calories (g/d)	600 (50)	350 (29) [7]
Hepatitis B virus		
Seropositivity for hepatitis B surface antigen, blood donors' cohort, 1991–1993 [37]	No infection	
Hepatitis C virus		
Seropositivity for antibody to hepatitis C, blood donors' cohort, 1991–1993 [37]	No infection	
<i>H. pylori</i>		
Seropositivity for anti- <i>H. pylori</i> immunoglobulin G, multi-center study, late 1990s [38]	No infection	

Values are means, with standard deviations in parentheses.

^aWe obtained exposure data from the 2007 National Health and Nutrition Survey [28] unless stated otherwise.

^bThe optimal category for liver cancer and suicide was "occasional drinkers" because previous studies used it as the reference category for estimation of relative risks.
doi:10.1371/journal.pmed.1001160.t002

$$\begin{aligned} \text{Fasting plasma glucose (mg/dl)} = \\ -9.2 + 21.9 \times \text{hemoglobin A1c}_{\text{JDS}} (\%) \end{aligned} \quad (3)$$

where hemoglobin A1c_{JDS} is a value standardized by calibrators provided by the Japan Diabetes Society and lower than an internationally used value by around 0.4% [29]. As a minor adjustment, we further deducted from this equation a difference in means between predicted fasting plasma glucose and measured casual plasma glucose among 165 participants in the 2007 NHNS who had fasted for more than 8 h (6.4 mg/dl).

In the NHNS, health care professionals measured the blood pressure of seated persons in their right upper arm after 5 min of rest, using a Riva-Rocci mercury manometer. For a trend analysis of cardiovascular mortality attributable to high blood pressure, which is described below, we used the National Nutrition Surveys for 1980–2002 and the NHNS for 2003–2007. These surveys took only one blood pressure measurement per individual until starting

to collect two measurements per individual in the 2000 survey. We therefore used a single measurement for the surveys in 1980–1999 and the second measurement for the 2000–2007 surveys. We excluded pregnant or breastfeeding women from the analysis of blood pressure.

For dietary risk exposure variables, dietitians visited households to distribute questionnaires and explain the survey method for diet and lifestyle. Household representatives weighed and recorded the quantity of each food item consumed for one day (excluding holidays). Dietitians visited households again during the survey period to check and correct completed questionnaires. We estimated intakes of dietary trans fatty acids using conversion factors of food items provided by the Cabinet of Japan Food Safety Committee [31]. Considering that nutrition intakes are correlated with energy intake determined by body size, physical activity, and metabolic efficiency, we adjusted intakes of fruit, vegetables, and dietary sodium for total energy intake with a simple linear regression equation having nutrient intake as a dependent variable and total caloric intake as an

Table 3. Exposure to risk factors by sex and age group in 2007.

Sex, Risk Factor	Age														
	30–44 y			45–59 y			60–69 y			70–79 y			≥80 y		
	<i>n</i> ^a	Mean	SE												
Men															
Fasting plasma glucose (mmol/l)	300	5.4	0.1	374	5.7	0.0	411	6.0	0.1	339	5.9	0.0	107	5.9	0.1
LDL cholesterol (mmol/l)	300	3.3	0.0	375	3.4	0.0	413	3.1	0.0	340	3.0	0.0	108	2.9	0.1
Systolic blood pressure (mm Hg)	312	124.2	0.8	394	133.9	0.9	427	140.9	0.9	359	142.2	1.0	116	144.1	1.8
Body mass index (kg/m ²)	673	23.9	0.1	777	23.8	0.1	620	23.8	0.1	470	23.6	0.2	155	22.6	0.3
Dietary TFA (% of total calories)	806	0.3	0.0	858	0.3	0.0	664	0.2	0.0	517	0.2	0.0	179	0.3	0.0
Dietary PUFA (% of total calories)	806	5.7	0.1	858	5.6	0.1	664	5.3	0.1	517	5.1	0.1	179	5.0	0.1
Dietary SFA (% of total calories)	806	6.8	0.1	858	6.2	0.1	664	5.7	0.1	517	5.6	0.1	179	5.9	0.2
Dietary salt intake (g/d)	806	11.4	0.2	858	12.3	0.2	664	12.6	0.2	517	12.2	0.2	179	10.9	0.3
Fruit and vegetable intake (g/d)	804	288.6	6.0	856	342.5	6.6	663	432.3	8.8	515	446.8	9.6	178	463.5	15.9
Never or former drinkers (%) ^b	850	26.6	1.5	950	25.9	1.4	699	28.9	1.7	525	40.8	2.1	184	55.4	3.7
Alcohol-related accidents/four-wheel vehicle road traffic accidents, 2004 (%) [40] ^c		1.7		1.7			1.7			1.7			1.7		
Have intense physical activity (%)	808	34.8	1.7	869	34.5	1.6	667	28.8	1.8	518	42.1	2.2	179	21.8	3.1
Never or former smokers (%)	850	45.2	1.7	946	53.6	1.6	698	65.9	1.8	524	78.6	1.8	184	82.1	2.8
Smoking impact ratio		0.0		0.6			0.5			0.5			0.7		
Hepatitis B virus (%) [37]		0.9		0.9			0.9			0.6			0.6		
Hepatitis C virus (%) [37]		0.6		1.6			2.6			7.9			7.9		
<i>H. pylori</i> (%) [38]		23.6		47.4			66.1			73.4			72.6		
Women															
Fasting plasma glucose (mmol/l)	563	5.3	0.0	620	5.7	0.0	523	5.9	0.0	408	5.9	0.0	154	5.9	0.1
LDL cholesterol (mmol/l)	565	2.9	0.0	622	3.4	0.0	523	3.5	0.0	410	3.3	0.0	154	3.2	0.1
Systolic blood pressure (mm Hg)	527	112.4	0.6	652	128.1	0.8	560	135.8	0.8	433	138.9	0.8	170	143.2	1.4
Body mass index (kg/m ²)	874	21.4	0.1	905	22.7	0.1	723	23.3	0.1	534	23.1	0.2	248	22.4	0.3
Dietary TFA (% of total calories)	955	0.4	0.0	957	0.3	0.0	762	0.3	0.0	561	0.3	0.0	285	0.2	0.0
Dietary PUFA (% of total calories)	955	5.9	0.1	957	6.0	0.1	762	5.6	0.1	561	5.3	0.1	285	5.3	0.1
Dietary SFA (% of total calories)	955	7.8	0.1	957	7.0	0.1	762	6.2	0.1	561	5.9	0.1	285	5.7	0.2
Dietary salt intake (g/d)	955	9.6	0.1	957	10.7	0.1	762	10.9	0.2	561	10.6	0.2	285	10.0	0.2
Fruit and vegetable intake (g/d)	951	346.0	6.1	957	460.2	7.6	761	541.3	9.0	561	522.8	9.7	284	490.3	13.2
Never or former drinkers (%) ^b	1,014	54.9	1.6	1,047	61.1	1.5	795	75.5	1.5	579	83.4	1.5	310	88.7	1.8
Alcohol-related accidents/four-wheel vehicle road traffic accidents, 2004 (%) [40] ^c		1.7		1.7			1.7			1.7			1.7		
Have intense physical activity (%)	958	36.3	1.6	959	40.9	1.6	765	39.0	1.8	562	45.4	2.1	286	21.3	2.4
Never or former smokers (%)	1,014	81.8	1.2	1,047	87.1	1.0	794	92.1	1.0	579	96.5	0.8	310	95.5	1.2
Smoking impact ratio		0.0		0.1			0.2			0.2			0.2		
Hepatitis B virus (%) [37]		0.5		0.5			0.5			0.6			0.6		
Hepatitis C virus (%) [37]		0.4		1.6			3.5			7.0			7.0		
<i>H. pylori</i> (%) [38]		23.6		47.4			66.1			73.4			72.6		

^aSample size in the National Health and Nutrition Survey in 2007.

^bFor those aged 20–29 y, the mean (standard error) was 40.4 (2.7) in men (*n* = 324) and 53.9 (2.5) in women (*n* = 395).

^cReported for the total age group of both sexes combined.

PUFA, polyunsaturated fatty acids; SE, standard error; SFA, saturated fatty acids; TFA, trans fatty acids.

doi:10.1371/journal.pmed.1001160.t003

independent variable [32]. Calorie-adjusted nutrient intakes were computed as the sum of residuals from the regression model and the expected nutrient intake for a person with mean caloric intake.

We used a smoking impact ratio as a more reliable indicator of accumulated exposure to tobacco smoking than the prevalence of current smokers. The smoking impact ratio was defined as total lung cancer mortality in excess of never-smokers in a study

population relative to the excess lung cancer mortality among current smokers in a reference population [33,34]. We used the following formula to calculate smoking impact ratios by age group and sex:

$$\text{Smoking impact ratio} = \frac{C_{LC} - N_{LC}}{S_{LC}^* - N_{LC}^*} \times \frac{N_{LC}^*}{N_{LC}}, \quad (4)$$

where C_{LC} and N_{LC} denote lung cancer mortality of the total population and never-smokers, respectively, in a study population (i.e., the Japanese population), and S_{LC}^* and N_{LC}^* signify lung cancer mortality among current smokers and never-smokers, respectively, in a reference population. We obtained total lung cancer mortality from the redistributed data of vital records described above. Our reference population was residents included in a pooled study of three large-scale cohorts in Japan [15,35,36]. Because we also adopted never-smokers' lung cancer mortality in the Japanese population from this pooled study, N_{LC} and N_{LC}^* were equivalent to each other in our analysis.

We obtained data on the prevalence of infections with hepatitis B and C viruses and the bacterium *H. pylori* from epidemiological studies undertaken in Japan in the 1990s [37,38]. Assuming that infection rates do not vary within birth cohorts over time, we applied infection rates by age group in the 1990s to those of corresponding age in 2007. For example, the infection rate for hepatitis B virus in men aged 60–69 y in 2007 was that of men aged 45–54 y in 1991–1993. We considered that all deaths from cervix uteri cancer and adult T-cell lymphoma/leukemia were caused by infections with human papillomavirus and HTLV-1, respectively [26,39].

In order to measure exposure levels of alcohol use related to deaths from road traffic injuries, we employed a proportion of alcohol-impaired driving, which was defined as driving with breath alcohol concentrations above 0 mg/l, to the total number of cases of road traffic accidents involving four-wheeled vehicles and motorcycles in 2004 (1.7%). We obtained this figure from a past study on alcohol concentrations in the breath of drivers, which used a national dataset prepared by the Japan Institute for Traffic Accident Research and Data Analysis [40].

Selection of Relative Risks

Tables S1, S2, S3, S4, S5, S6, S7 provide details of relative risks used in this analysis. We conducted a literature review of prospective studies evaluating effects of risk factors on cause-specific deaths in Japan. Strategies for the database search involved contacting authors of key reports and leading experts in the field, and we critically appraised the identified literature. Our motive for undertaking the literature search was to identify evidence from past studies in the Japanese population to be backed up with pooled evidence establishing causalities or associations from the Global Burden of Disease Study [20]. Criteria for the selection of evidence for the Japanese population were: (i) pooled or individual estimates from large-scale prospective observational studies and (ii) confirming causalities or associations that had been already established in past studies. When there was no study for the Japanese population satisfying these conditions, we sought evidence from the Asia-Pacific Cohort Studies Collaboration. If we could not find evidence from this source, then we adopted relative risks identified in the Global Burden of Disease Study. We considered relative risks to be null if they were statistically insignificant. In addition, we had to restrict the source of evidence on relative risks for tobacco smoking to the pooled analysis of large-scale cohorts in Japan, because we used their estimates of

current smokers' and never-smokers' lung cancer mortality of a reference population to calculate smoking impact ratios. We excluded mortality from tuberculosis and diabetes mellitus associated with tobacco smoking, because the studies did not examine these causes.

Counterfactual Distributions of Risk Exposures

As an alternative distribution of risk exposures, we used an optimal distribution in which harmful effects of each risk factor on morbidity and mortality would be minimized in a population (i.e., a theoretical-minimum-risk exposure distribution). With the exception of infections, we obtained information on theoretical-minimum-risk exposure distributions from a previous study in the United States (Table 2) [20].

In the analysis of gains in life expectancy and probabilities of death, we also investigated alternative counterfactual distributions of risk exposures that followed recommendations of clinical guidelines and goals of Health Japan 21. This analysis enabled quantification of potential health gains that would be more realistic than theoretical minimums. We included risk factors in this part of our analysis only if specific control targets were available from these sources and units of measurement corresponded to those of relative risks (Table 2). In order to obtain counterfactual distributions for numerical risks, we used their control threshold as the mean and applied the coefficient of variation to estimate the standard deviation.

The relationship between dietary salt intake and cardiovascular mortality was based on a convincing effect of high dietary salt on systolic blood pressure that was estimated from a meta-analysis of dietary trials (Table S6) [20]. In order to obtain hazards of excess dietary salt intake on cardiovascular death, we first estimated the decrease in systolic blood pressure associated with a reduction in dietary salt intake to individual optimal levels and then applied relative risks of high systolic blood pressure for relevant cardiovascular diseases (Table S1).

Effects on Life Expectancy and Probabilities of Death

We translated mortality changes into gains in life expectancy at 40 y of age to understand the potential impact of the management of risk factors on longevity. We constructed life tables using observed age-specific mortality rates and mortality that would be expected if risk factor exposures were controlled at alternative levels. We took the differences between these values as showing life expectancy gains that would occur when shifting from an actual risk factor exposure to a counterfactual. We also calculated effects on probabilities of dying between the ages of 15 and 60 y ($_{45}q_{15}$) and between 60 and 75 y ($_{15}q_{60}$).

Joint Effects of Multiple Risk Factors for Cardiovascular Mortality

We estimated joint effects of multiple risk factors on excess mortality from cardiovascular diseases and the additional life expectancy at age 40 y that would be achieved under counterfactual distributions. Risk factors included in this part of the analysis were high body mass index, high blood pressure, and high concentrations of blood glucose and low density lipoprotein (LDL) cholesterol. We took account of high dietary sodium intake to compensate for its indirect effect through elevated blood pressure, using the steps described above. We also adopted a 50% reduction of the excess risk of high body mass index on cardiovascular deaths to incorporate a mediation of its associations through other risk factors [21]. We used an additive excess risk scale to correct for correlations of these risk factors and calculate joint relative risks at

the individual level. This approach has been described in detail elsewhere [21]. We summed the combined relative risks for individual records to compute population-attributable fractions for the joint effects of these cardiovascular risks.

Long-Term Trends in Attributable Deaths

To examine contributions of the management of modifiable risk factors to the improvement of life expectancy over time, we estimated the number of deaths from cancers attributable to tobacco smoking and deaths from stroke associated with high blood pressure from 1980 to 2007. We employed the algorithm described above to obtain consistent mortality data throughout this period, from which we used total lung cancer mortality in each year to calculate smoking impact ratios over time. For the analysis of high blood pressure and stroke, we excluded people over 80 y of age because the sample size was insufficient. We also incorporated the above-mentioned mediated effects of dietary sodium intake through raised blood pressure at the individual level.

Uncertainty Analyses

We conducted statistical simulation to deal with the uncertainty that was introduced by using sample estimates for risk exposures and relative risks [41]. To account for sampling variability, we randomly drew 1,000 sets of values of all components based on samples. In each sequential step of the simulation, we drew for each age–sex group: (i) a random sample of participants in the 2007 NHNS with replacement to obtain the original sample size of those who had no missing value for each risk factor, (ii) a relative risk for each risk–disease pair from a log-normal distribution with means and standard deviations reported in epidemiological studies, (iii) coefficients of the regression of hemoglobin A1c on fasting plasma glucose from a normal distribution with standard deviations that we calculated from information given in a past study (1.0 for the constant term and 0.2 for the coefficient of hemoglobin A1c) [30], (iv) the difference in means between predicted fasting plasma glucose and measured casual plasma glucose in the 2007 NHNS from a normal distribution with mean of 6.4 mg/dl and standard deviation of 1.1 mg/dl that we estimated from the survey data, (v) the proportion of the excess risk of body mass index mediated through systolic blood pressure and fasting plasma glucose from a normal distribution with mean of 0.5 and standard deviation of 0.1 [21], and (vi) lung cancer mortality of current smokers and never-smokers from a normal distribution with means and standard deviations estimated from the pooled analysis of Japanese cohorts [15,35]. We used each sampled set of risk exposures and relative risks to compute population-attributable fractions, mortality attributable to each risk factor or a combination of risk factors, and changes in life expectancy under counterfactual distributions. We defined a 95% confidence interval (CI) by a span across the estimates of each outcome at the 2.5th and 97.5th percentiles of the 1,000 simulations.

Results

Contributions of Health Risks to Cause-Specific Mortality in 2007

Tables S8 and S9 provide population-attributable fractions of the 16 modifiable risk factors and a combination of physiological risk factors for mortality from non-communicable diseases and injuries by age group and sex in 2007. These fractions cannot be summed across risk factors for a single cause of death, because causal relationships between risk factors are not considered in the analysis of individual risk factors.

Under the theoretically minimum counterfactuals listed in Table 2, tobacco smoking and high blood pressure were the two major single contributors to the number of deaths from non-communicable diseases and injuries (Table 4). Among the total of 960,000 deaths from causes included in this study, tobacco smoking was associated with 129,000 deaths (95% CI: 115,000–154,000). Approximately three-quarters of these deaths occurred in men (95,000 deaths, 95% CI: 88,000–103,000), although the attributable mortality was still substantial for women (34,000 deaths, 95% CI: 23,000–57,000). In men, 70% of deaths attributable to this risk factor were caused by cancers and took place among those aged 45–79 y. In women, cardiovascular diseases and cancers accounted for 42% and 36%, respectively, of the mortality attributable to tobacco smoking. By disease subtypes for sexes combined, lung cancer was the leading cause (42,000 deaths, 95% CI: 39,000–45,000), followed by ischemic heart disease (27,000 deaths, 95% CI: 19,000–42,000) and chronic obstructive pulmonary disease (13,000 deaths, 95% CI: 9,000–16,000).

High blood pressure was associated with 104,000 cardiovascular deaths (95% CI: 86,000–119,000) in 2007. This was the greatest risk factor for cardiovascular mortality of all risk factors included in this analysis, and the mortality burden was shared evenly between the sexes. A majority of deaths attributable to high blood pressure occurred among people aged 70 y and over (85,000 deaths) and were caused by stroke (47,000 deaths, 95% CI: 38,000–56,000) or ischemic heart disease (28,000 deaths, 95% CI: 15,000–39,000).

Although the numbers of attributable deaths for other physiological, lifestyle, dietary, and infectious factors were small when compared to those for tobacco smoking and high blood pressure, most of these other factors were associated with tens of thousands of deaths from non-communicable diseases and external causes. Physical inactivity was associated with 52,000 deaths (95% CI: 47,000–58,000), and 75% of them occurred among people aged 70 y and older. Ischemic heart disease was the major cause of mortality attributable to this risk factor (31,000 deaths, 95% CI: 28,000–35,000). High blood glucose was associated with 34,000 deaths (95% CI: 26,000–43,000), of which 75% occurred among people aged 70 y and over and 68% were caused by ischemic heart disease. High dietary salt intake was associated with 19,000 cardiovascular deaths (95% CI: 16,000–22,000), which were included in cardiovascular mortality attributable to high blood pressure, and there were 15,000 deaths from stomach cancer (95% CI: 9,000–20,000). Seventy-six percent of deaths attributable to this risk factor occurred among people aged 70 y and over.

Alcohol use was associated with 31,000 deaths (95% CI: 27,000–35,000) from non-communicable diseases and injuries, 84% of which occurred among men. A major cause of death attributable to this risk factor was liver cirrhosis (11,000 deaths, 95% CI: 10,000–12,000), followed by liver cancer (6,000 deaths, 95% CI: 4,000–8,000), esophagus cancer (5,000 deaths, 95% CI: 4,000–5,000), and colon cancer (4,000 deaths, 95% CI: 4,000–5,000). Alcohol use was associated with 3,000 (95% CI: 2,000–5,000) out of 83,000 deaths of people aged 20 y and over from external causes included in this study. Two thousand deaths were from suicide (95% CI: 1,000–4,000), and there were fewer than 1,000 deaths each attributable to falls, road traffic accidents, homicide, and other injuries. Most of the suicide deaths attributable to alcohol use occurred among men, particularly those aged 30 to 59 y (71%).

Infection with *H. pylori* was associated with 31,000 deaths from gastric cancer in 2007 (95% CI: 27,000–34,000). Seventy-two

Table 4. The number of deaths attributable to risk factors in Japan, 2007 (in thousands).

Sex, Risk Factor	Total	Cardiovascular	Cancer	Diabetes Mellitus	Respiratory	Other NCD	Injuries
Sexes combined							
High blood glucose	34.1 (26.4, 43.1)	27.2 (19.5, 36.2)		6.9			
High LDL cholesterol	23.9 (16.7, 31.2)	23.9 (16.7, 31.2)					
High blood pressure	103.9 (86.0, 119.1)	103.9 (86.0, 119.1)					
High body mass index	19.0 (16.1, 21.9)	13.8 (11.1, 16.4)	4.1 (3.4, 4.9)	1.1 (0.8, 1.3)			
Alcohol use	30.6 (27.5, 34.7)	-2.0 (-4.0, 0.0)	18.2 (16.2, 20.8)	-0.1 (-0.1, -0.1)		11.6 (10.6, 12.7)	2.9 (1.9, 4.6)
Tobacco smoking	128.9 (115.5, 153.6)	33.4 (25.4, 48.8)	77.4 (72.3, 83.9)		18.1 (12.6, 26.4)		
Physical inactivity	52.2 (46.7, 57.7)	42.2 (36.6, 47.6)	9.3 (8.5, 10.0)	0.7 (0.6, 0.9)			
High TFA intake	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)					
Low PUFA intake	21.2 (8.1, 38.7)	21.2 (8.1, 38.7)					
High dietary sodium intake	34.0 (27.3, 39.4)	19.0 (16.1, 22.3)	14.9 (8.8, 19.6)				
Low fruit and vegetable intake	8.9 (6.7, 10.8)	5.1 (3.3, 6.7)	3.8 (2.5, 4.9)				
Hepatitis B virus	11.6 (9.8, 13.5)		11.6 (9.8, 13.5)				
Hepatitis C virus	23.0 (21.3, 24.5)		23.0 (21.3, 24.5)				
<i>H. pylori</i>	30.6 (27.2, 33.5)		30.6 (27.2, 33.5)				
Human papillomavirus	2.6		2.6				
HTLV-1	1.1		1.1				
Joint risk ^a	157.0 (144.0, 173.4)	157.0 (144.0, 173.4)					
Men							
High blood glucose	17.2 (12.7, 22.2)	14.3 (9.8, 19.3)		2.9			
High LDL cholesterol	12.2 (8.1, 15.9)	12.2 (8.1, 15.9)					
High blood pressure	50.1 (39.9, 58.5)	50.1 (39.9, 58.5)					
High body mass index	12.1 (10.0, 14.3)	9.6 (7.6, 11.6)	2.0 (1.6, 2.6)	0.5 (0.4, 0.7)			
Alcohol use	25.8 (22.6, 29.5)	-1.7 (-3.7, 0.2)	15.9 (13.7, 18.2)	-0.1 (-0.1, -0.1)		9.0 (8.2, 9.7)	2.8 (1.7, 4.4)
Tobacco smoking	94.9 (87.7, 103.4)	19.3 (15.4, 24.5)	66.5 (61.8, 71.2)		9.1 (6.8, 10.9)		
Physical inactivity	25.9 (22.8, 29.4)	21.0 (18.1, 24.4)	4.6 (4.0, 5.1)	0.3 (0.3, 0.4)			
High TFA intake	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)					
Low PUFA intake	12.0 (5.3, 29.3)	12.0 (5.3, 29.3)					
High dietary sodium intake	18.4 (13.0, 22.7)	8.8 (7.3, 10.2)	9.7 (4.4, 13.7)				
Low fruit and vegetable intake	7.6 (5.5, 9.5)	4.3 (2.5, 5.9)	3.3 (2.1, 4.4)				
Hepatitis B virus	8.0 (6.6, 9.6)		8.0 (6.6, 9.6)				
Hepatitis C virus	14.8 (13.4, 16.1)		14.8 (13.4, 16.1)				
<i>H. pylori</i>	20.0 (17.0, 22.4)		20.0 (17.0, 22.4)				
HTLV-1	0.6		0.6				
Joint risk ^a	78.5 (70.8, 87.8)	78.5 (70.8, 87.8)					
Women							
High blood glucose	16.9 (11.6, 23.3)	12.9 (7.6, 19.3)		4.0			
High LDL cholesterol	11.7 (6.5, 18.0)	11.7 (6.5, 18.0)					
High blood pressure	53.9 (40.0, 66.9)	53.9 (40.0, 66.9)					
High body mass index	6.8 (5.0, 8.9)	4.2 (2.5, 5.9)	2.1 (1.6, 2.6)	0.5 (0.3, 0.8)			
Alcohol use	4.8 (3.8, 6.3)	-0.3 (-0.5, -0.1)	2.3 (1.7, 3.3)	-0.0 (-0.1, -0.0)		2.6 (2.1, 3.4)	0.2 (0.1, 0.3)
Tobacco smoking	34.0 (22.9, 56.5)	14.1 (7.3, 28.2)	10.9 (8.3, 15.7)		9.0 (4.0, 17.4)		
Physical inactivity	26.3 (21.6, 30.9)	21.2 (16.5, 25.9)	4.7 (4.2, 5.2)	0.4 (0.3, 0.5)			
High TFA intake	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)					
Low PUFA intake	9.3 (4.0, 16.1)	9.3 (4.0, 16.1)					
High dietary sodium intake	15.6 (11.3, 19.2)	10.3 (7.7, 13.1)	5.3 (1.9, 7.5)				

Table 4. Cont.

Sex, Risk Factor	Total	Cardiovascular	Cancer	Diabetes Mellitus	Respiratory	Other NCD	Injuries
Low fruit and vegetable intake	1.3 (0.9, 1.7)	0.8 (0.4, 1.2)	0.5 (0.3, 0.6)				
Hepatitis B virus	3.6 (2.8, 4.5)		3.6 (2.8, 4.5)				
Hepatitis C virus	8.2 (7.3, 9.0)		8.2 (7.3, 9.0)				
<i>H. pylori</i>	10.6 (8.9, 12.0)		10.6 (8.9, 12.0)				
Human papillomavirus	2.6		2.6				
HTLV-1	0.5		0.5				
Joint risk ^a	78.5 (66.9, 91.1)	78.5 (66.9, 91.1)					

Values in parentheses indicate lower and upper bounds of 95% CI.

^aA combination of high blood glucose, high LDL cholesterol, high blood pressure (directly, and indirectly through high dietary salt intake), and high body mass index. NCD, non-communicable disease; PUFA, polyunsaturated fatty acids, TFA, trans fatty acids.

doi:10.1371/journal.pmed.1001160.t004

percent of these deaths occurred among people aged 70 y and older. Infection with hepatitis C virus was associated with 23,000 deaths from liver cancer (95% CI: 21,000–24,000). Forty-five percent of these deaths were in people aged 70–79 y, including those born in the early 1930s. For both *H. pylori* and hepatitis C virus infections, around 65% of the attributable mortality took place in men.

High LDL cholesterol was associated with 24,000 cardiovascular deaths (95% CI: 17,000–31,000), largely from ischemic heart disease (23,000 deaths, 95% CI: 16,000–30,000). Low dietary intake of polyunsaturated fatty acids was associated with 21,000 deaths from ischemic heart disease (95% CI: 8,000–39,000), and 47% of these deaths occurred among people aged 80 y and over. High body mass index was associated with 19,000 deaths (95% CI: 16,000–22,000): 64% of these deaths occurred in men, and ischemic heart disease was the major cause (11,000 deaths, 95% CI: 8,000–13,000).

If systolic blood pressure (directly, and indirectly through dietary salt intake), blood glucose, LDL cholesterol, and body mass index were controlled jointly to their optimal distributions, i.e., theoretical-minimum-risk exposure distributions, 157,000 cardiovascular deaths would have been prevented in 2007 (95% CI: 144,000–173,000). The mortality burden attributable to the combination of these risks was shared equally between the sexes, and a majority of the burden occurred among people aged 70 y and older.

Effects of Risk Factors on Life Expectancy and Probabilities of Death

Japanese life expectancy at age 40 y was 40.4 y for men and 46.8 y for women in 2007 [3]. Figure 1 illustrates gains in life expectancy at age 40 y and percentage changes in probabilities of death that would have been expected in 2007 if risk factors had been controlled to their theoretically minimum distributions individually or jointly with others. For men, tobacco smoking was associated with the largest potential increase in life expectancy at age 40 y (1.8 y, 95% CI: 1.6–1.9), followed by a joint effect of multiple physiological factors (1.4 y, 95% CI: 1.3–1.6) and single effects of high systolic blood pressure (0.9 y, 95% CI: 0.7–1.0) and alcohol use (0.5 y, 95% CI: 0.5–0.6). A considerable part of the smoking effect (1.2 y, 95% CI: 1.1–1.3) was accounted for by an expected associated fall in cancer mortality through a decrease in probabilities of dying between the ages of 15 and 60 (45q15) by 8% (95% CI: 7–10) and between the ages of 60 and 75 (15q60) by 13% (95% CI: 12–14). A drop in cardiovascular mortality through

the joint control of multiple risks was associated with an expected percentage decrease of 13% (95% CI: 12–15) in 45q15 and 11% (95% CI: 10–13) in 15q60, while controlling high blood pressure was associated with an expected fall of 7% both in 45q15 (95% CI: 6–8) and 15q60 (95% CI: 5–8). Decreasing alcohol use was associated with an expected percentage decrease of 9% (95% CI: 7–11) in 45q15 and 5% (95% CI: 5–6) in 15q60 for men. A substantial part of the potential change in the probability of death among young and middle-aged men through moderate drinking was explained by a fall in mortality from other non-communicable diseases including liver cirrhosis and liver cancer (4%, 95% CI: 4–4) and injuries (2%, 95% CI: 1–4).

For women, controlling systolic blood pressure and tobacco smoking to optimal counterfactuals would have extended life expectancy at age 40 y by 0.9 y (95% CI: 0.7–1.1) and 0.6 y (95% CI: 0.4–1.0), respectively. The impact of tobacco smoking on a probability of death in older women was estimated to be 8% (95% CI: 5–13), which was comparable to that of high blood pressure (7%, 95% CI: 6–8). A joint effect of cardiovascular risk factors on female life expectancy at age 40 y was estimated to be 1.4 y (95% CI: 1.2–1.7), with a decrease in probability of death of 8% (95% CI: 7–10) for younger adults and 11% (95% CI: 10–12) for older ages.

Table 5 shows changes in life expectancy at age 40 y and probabilities of death under the more practical counterfactuals defined by clinical guideline recommendations and national goals. Overall, the gains were less than half of those under theoretically minimum distributions. In both sexes, life expectancy at age 40 y would have increased by 0.7 y (95% CI: 0.6–0.9) through the joint control of cardiovascular risks and by 0.4 y (95% CI: 0.3–0.5) through reducing systolic blood pressure to the distribution recommended by clinical guidelines.

Trends in Mortality Attributable to Tobacco Smoking and High Blood Pressure in 1980–2007

Figure 2 illustrates trends in the number of deaths from cancers that were attributable to tobacco smoking from 1980 to 2007. A continuous increase has been observed in men over 70 y old and women over 80 y old. A fall after a peak around 1995 among men aged 60–69 y reflected the fact that the lifetime smoking prevalence reached a peak in the birth cohort of the late 1920s and decreased in the cohort of the late 1930s [42]. This effect manifested again as a peak in attributable cancer mortality around 2005, when the birth cohort of the late 1920s was 70–79 y old. A temporary halt in the increase of cancer deaths attributable to

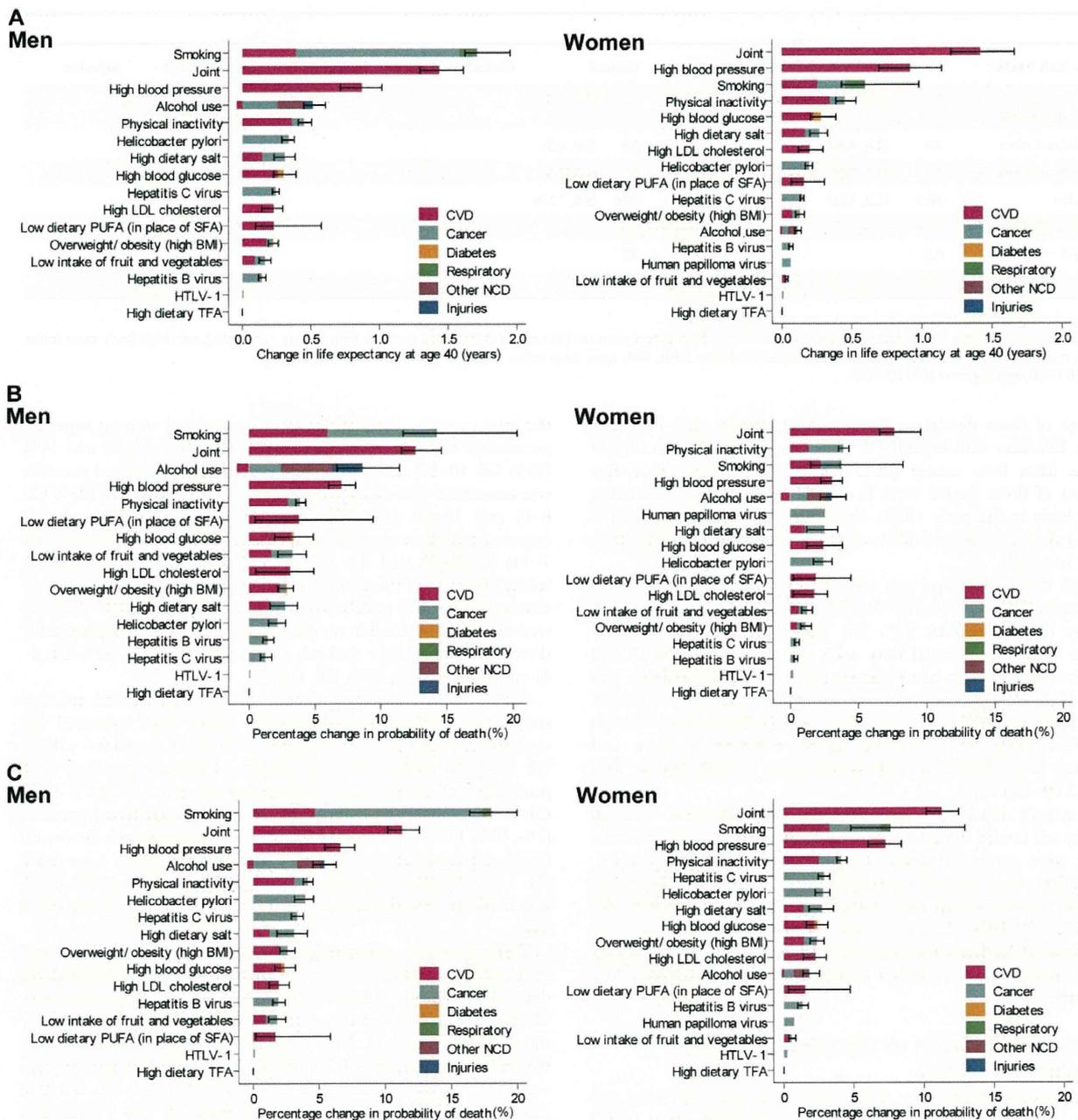


Figure 1. Changes in life expectancy at age 40 y and the probability of death under optimal distributions of risk factors in Japan, 2007. (A) Life expectancy at age 40. (B) Probability of death between 15 and 60 y of age. (C) Probability of death between 60 and 75 y of age. Joint risk is a combination of high blood pressure (directly, or indirectly through high dietary salt intake), high blood glucose, high LDL cholesterol, and high body mass index. BMI, body mass index; CVD, cardiovascular disease; NCD, non-communicable diseases; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TFA, trans fatty acids. doi:10.1371/journal.pmed.1001160.g001

tobacco smoking for men over 80 y old in the early 2000s reflected a reduction in this population group as a result of the 1918 influenza pandemic.

Figure 3 demonstrates trends in the number of deaths from stroke that were attributable to high blood pressure. Stroke deaths

associated with this risk factor, either directly or indirectly through high dietary sodium intake, consistently declined for both sexes under 80 y of age. This favorable trend continued in the 2000s for women and for men under the age of 60 y, but it ceased for elderly men by the mid-1990s.

Table 5. Changes in life expectancy at age 40 y (e40) and percentage changes in the probability of death between 15 and 60 y of age (45q15) and between 60 and 75 y of age (15q60) under counterfactual distributions of risk factors defined by clinical guidelines and national goals.

Risk Factor	e40 (Years)		45q15 (Percent)		15q60 (Percent)	
Men						
High blood glucose	0.1	(0.0, 0.2)	-0.1	(-1.0, -0.1)	-0.7	(-1.2, -0.2)
High LDL cholesterol	0.0	(0.0, 0.0)	-0.6	(-1.3, -0.1)	0.0	(-0.1, 0.0)
High blood pressure	0.4	(0.3, 0.5)	-1.2	(-2.1, -0.3)	-3.0	(-3.7, -2.3)
High body mass index	0.1	(0.1, 0.2)	-1.8	(-2.2, -1.4)	-1.6	(-2.0, -1.2)
High dietary salt intake	0.0	(0.0, 0.0)	-3.4	(-0.2, 0.0)	-2.4	(-0.5, -0.1)
Low fruit and vegetable intake	0.0	(0.0, 0.0)	-0.5	(-0.9, -0.3)	0.0	(0.0, 0.0)
Joint risk ^a	0.7	(0.6, 0.9)	-5.8	(-8.4, -5.1)	-6.0	(-7.4, -5.2)
Women						
High blood glucose	0.1	(0.1, 0.2)	-0.2	(-0.9, 0.0)	-0.7	(-1.2, -0.2)
High LDL cholesterol	0.0	(0.0, 0.0)	-0.4	(-0.8, 0.0)	-0.4	(-0.7, -0.3)
High blood pressure	0.4	(0.3, 0.5)	0.0	(0.0, 0.0)	-2.8	(-3.5, -2.1)
High body mass index	0.0	(0.0, 0.1)	-0.1	(-0.4, 0.0)	-1.1	(-1.5, -0.8)
High dietary salt intake	0.0	(0.0, 0.0)	-0.2	(-0.3, -0.1)	-0.4	(-0.5, -0.2)
Low fruit and vegetable intake	0.0	(0.0, 0.0)	0.0	(-0.1, 0.0)	0.0	(0.0, 0.0)
Joint risk ^a	0.7	(0.6, 0.9)	-3.1	(-2.6, -1.0)	-5.6	(-6.6, -4.9)

Values in parentheses indicate lower and upper bounds of 95% CI.

^aA combination of high blood glucose, high LDL cholesterol, high blood pressure (directly, and indirectly through high dietary salt intake), and high body mass index. doi:10.1371/journal.pmed.1001160.t005

Discussion

To our knowledge, this is the first study in Japan to assess and compare effects of a comprehensive list of modifiable risk factors on life expectancy and death from non-communicable diseases and injuries under the framework of comparative risk assessment. Our study indicates that major risks for adult mortality from these causes are tobacco smoking and high blood pressure, as well as a combination of multiple cardiovascular risks. We also demonstrate that, over the past 27 y, cancer mortality attributable to tobacco smoking has increased, especially in the older population, while stroke death associated with high blood pressure has decreased.

The leading single risk factors for adult mortality from non-communicable diseases and injuries in Japan, i.e., tobacco smoking, high blood pressure, physical inactivity, and high blood glucose concentrations, agree with those in the world and the US [2,20]. The number of deaths attributable to tobacco smoking for Japanese men is large relative to the number attributable to high blood pressure, even compared with the proportion among American men. This result may be related to a substantially higher prevalence of male smokers in Japan than in the US for the past 25 y [43]. Moreover, high body mass index ranks only tenth for both sexes in Japan, while it is one of the top five contributors to mortality in other high- and middle-income countries [2]. This finding reflects the fact that mean body mass index in Japan is low for the income level of the country [44].

Our estimate of the impact of tobacco smoking on male life expectancy at age 40 y (1.8 y) was smaller than those of past cohort studies in Japan. Previous studies showed that, according to smoking status at the time of the baseline survey, life expectancy for men aged 40 y in the total population was shorter than that of never-smokers by around 2.5 y [14,16]. Use of different exposure measurements may explain part of the difference in estimated impacts of tobacco smoking between the present and past studies.

We believe that the smoking impact ratio used in our study is useful for quantifying accumulated smoking risk over a lifetime.

Our results suggest that the threat of tobacco smoking for mortality is enormous in men and has been increasing over time through the accumulation of exposure to this risk in the older population. A previous study showed that lifetime smoking prevalence was low for the generation born in the late 1930s who experienced the deprivation in the early postwar years, but rose thereafter until it peaked for the birth cohort of the 1950s [42]. These findings imply that, without effective policy interventions, the increasing trend in tobacco-associated mortality may continue until at least the late 2030s, when the birth cohort of the late 1950s reaches the age of 80 y. Aiming to decrease the disease burden related to tobacco smoking in the population, the Japanese government enacted the Health Promotion Act in 2002 to support prevention of passive smoking in public places. Based on this legislation, Health Japan 21 specified four targets for tobacco smoking: (i) increasing knowledge of the adverse health effects of smoking, (ii) prohibiting minors from smoking, (iii) strengthening separation of smoking areas in public spaces and the workplace, and (iv) dissemination of smoking cessation programs in all municipalities. A final appraisal of Health Japan 21 concluded that there was improvement for all of these targets [7]. However, the prevalence of smoking in the male working population is still high at around 50%, although it has been gradually declining after the implementation of a series of antismoking policies. Moreover, although Japan ratified the World Health Organization Framework Convention on Tobacco Control in 2004, compliance is lagging behind international standards for smoke-free policies, bans on advertising, health warnings on cigarette packages, and antitobacco mass media campaigns [45]. The retail price of the most popular brand of cigarettes is lower than the average among high-income countries [45]. The recent tobacco tax increase in October 2010 was insufficient to induce smokers to give up

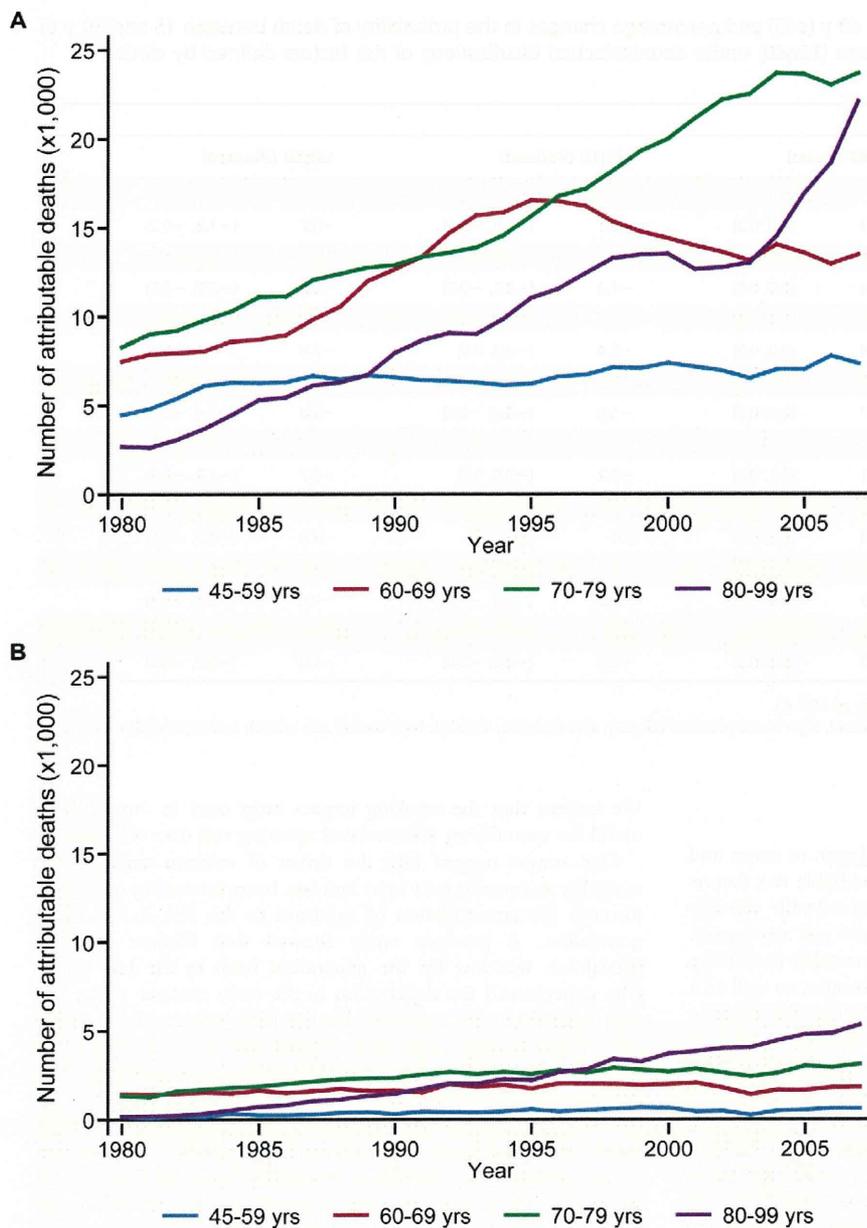


Figure 2. Cancer deaths attributable to tobacco smoking, by age group, 1980–2007. Data for (A) men and (B) women. doi:10.1371/journal.pmed.1001160.g002

purchasing tobacco products. Thus, the progress in tobacco control policies is slow, largely because Japanese society is relatively tolerant of this unhealthy behavior. In order to improve the health of the population, policymakers need to implement further stringent antismoking measures that appropriately assess the health impacts of smoking on non-smokers as well as on the smokers themselves.

Our study suggests that a decrease in population blood pressure partly accounts for a reduced mortality from stroke at least since 1980, although the downward trend leveled off for elderly men in the early 1990s. Stroke mortality started decreasing in the late 1960s and has been the major contributor

to the increase of life expectancy in Japan [4]; our finding backs up the idea that a reduction in population blood pressure has contributed to improved longevity. Potential key factors for the decline of blood pressure in the Japanese population may include increased use of blood-pressure-lowering drugs among patients with hypertension, and a reduction in dietary salt intake [46]. These successes may be attributed to the support of the national government for community-based programs for hypertension control that were proven to be effective in pilot studies conducted in the 1960s and 1970s [47]. In 1982, a national act on health and medical care was enacted that required all municipalities to provide residents aged 40 y and over with health screening and

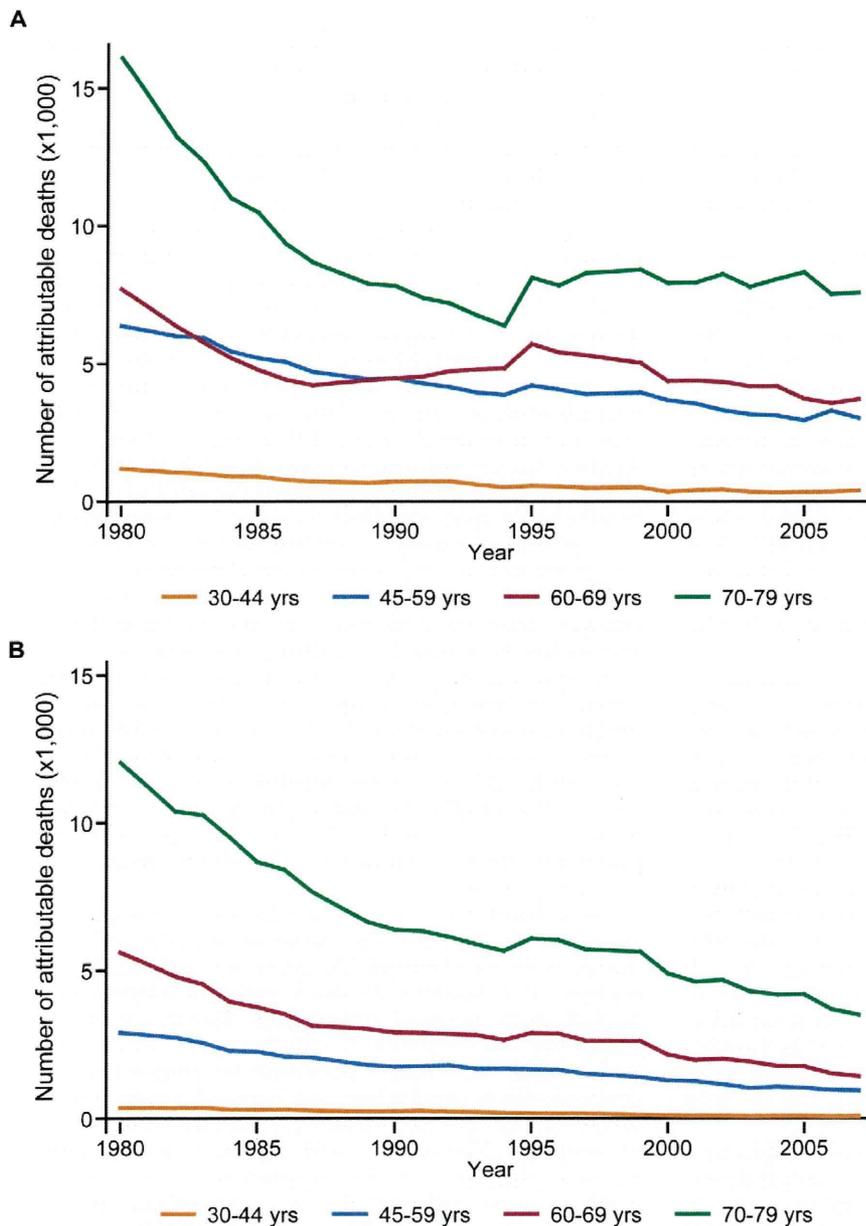


Figure 3. Stroke deaths attributable to high blood pressure, by age group, 1980–2007. Data for (A) men and (B) women. doi:10.1371/journal.pmed.1001160.g003

educational services for prevention of cardiovascular diseases [47].

Despite the decrease in stroke mortality attributable to high blood pressure, this is still the major risk factor for cardiovascular mortality in Japan. The management of high blood pressure is not adequate even under the practical standards of domestic clinical guidelines. In 2007, less than 60% of hypertensive patients took antihypertensive medication daily, and only 20% had their blood pressure controlled [48]. These treatment coverage and control rates are substantially lower than those in the US [48]. Previous studies pointed out that an acceptance of higher control thresholds of blood pressure among physicians [49] and insufficient treatment

regimens [50] might partly explain the poor control of blood pressure with antihypertensive drugs in Japanese clinical practice. A thorough investigation is necessary to understand what makes the quality of care for hypertension so low at the population level, including investigating adherence of patients to prescriptions. Furthermore, lowering dietary sodium intake is crucial for decreasing blood pressure as well as mortality from stomach cancer in Japan. The Japanese diet is traditionally high in salt, which mainly comes from soy sauce, miso soup, and salted vegetables and fish [51]. Although Health Japan 21 was successful in decreasing average daily salt intake from 13.5 g in the baseline year to 10.7 g in 2009 [7], it is well above the global target of 5 g/

d set by the World Health Organization [52]. Extra efforts by the industrial sector on ingredient labeling for consumers and reducing sodium content in commercially processed products are essential.

Another key finding of our study is that a considerable number of deaths from cardiovascular diseases would be prevented through joint control of multiple risk factors in Japan. In addition to the traditional approach of focusing on single risk factors, health education and effective treatment based on absolute risk have great potential for improving primary and secondary prevention of cardiovascular mortality. Our results support current domestic efforts to target high-risk populations, such as cardiovascular risk stratification according to categories of multiple risks [53,54] and the development of risk assessment charts for Japanese people [55].

Our study suggests that physical inactivity contributes to a substantial mortality from non-communicable diseases in Japan. Lack of exercise is common: in 2008, two-thirds of the Japanese adult population engaged in less than 30 min of moderate activity per week or less than 20 min of vigorous activity three times per week [56]. Considering global efforts to promote physical activity for the prevention of non-communicable diseases [57], it is important to strengthen policies for improving public understanding of the role of physical training in disease prevention, and provide support for individual's efforts to start having regular exercise.

Our results suggest that mortality from external causes, such as suicide and traffic accidents, associated with alcohol use is fairly small in Japan. For suicide, relative risks of alcohol use were insignificant, except for heavy drinking, in a large Japanese cohort study [58]. Major reasons for suicide in the male working population are psychiatric disorders and economic reasons such as business failure, unemployment, and debts [59], which suggest that direct risk factors for deaths from suicide are psychosocial, and alcohol use itself may have only an indirect effect. Regarding road traffic accidents, it remains to be seen in future research how robust our result is, because our information on road traffic accidents was limited to published crude estimates on risk exposures and relative risks. We also applied relative risks of suicide to falls, homicide, and other injuries because of the lack of evidence. In order to make a convincing argument on mortality from alcohol-related injuries in Japan, we need to wait for more detailed data and evidence to be accumulated and be made accessible.

One of distinctive characteristics of adult mortality in Japan is a large number of cancer deaths attributable to infectious agents, which is possibly common in East-Asian countries [26,60]. Mortality from stomach cancer related to *H. pylori* is substantial in Japan, because of the relatively high prevalence of this infection [26]. However, a decline in the prevalence of *H. pylori* infection was observed among people born after 1955 [38], who experienced improved hygienic conditions under rapid economic growth in early childhood. This favorable trend predicts a future reduction in the burden of gastric cancer attributable to *H. pylori* in Japan. Moreover, chronic infection from hepatitis C virus is responsible for the majority of cases of hepatocellular carcinoma in Japan, while hepatitis B virus plays the major role in most Asian countries [61]. A considerable part of mortality attributable to hepatitis C virus infection occurred among people born in the early 1930s. The risk of becoming infected with hepatitis viruses was high in this birth cohort, because intravenous use of methamphetamines was endemic in Japan in their young adulthood [27,62]. The spread of hepatitis viruses from drug abusers to the general population in the 1950s and 1960s was most likely mediated by transfusion of unscrubbed or commercial blood

and blood products and by medical practices such as needle sharing for immunizations [62]. The decreasing prevalence of infections with hepatitis C virus after the birth cohort of around 1935 indicates that the mortality burden of this infectious agent will diminish in the foreseeable future.

Will the estimated improvements in population health outcomes be worth all the efforts required of the government, citizens, and health care workers involved in the modification of risk factors? The overall increases in life expectancy associated with improved risk factor exposures may appear small in comparison with observed improvements in Japanese longevity over previous decades. This is, however, consistent with a past study's finding showing that even complete elimination of deaths from major causes would not affect life expectancy as much as anticipated in the US, and an additional drop in mortality would have only a marginal effect in countries where the rapid increases of life expectancy have already ended [63]. A study in Sweden also suggested that the main improvements in increasing a life span come from changes in death rates among the oldest groups [64]. In order for the aging population to continue the constant progress in longevity, it is essential to decrease mortality in older ages through the control of risk factors for non-communicable diseases and injuries. Working on risk factors in younger generations is especially important from this standpoint to ensure further improvement in Japanese life expectancy in the long run.

Our study was based on global efforts of various agencies to pool evidence on causality and consistency of relative risks. We also used Japanese population evidence from large-scale cohort studies if they confirmed established causality, although effects of excess risks should not vary across populations [20]. We believe, however, that our effort was justified because the pooled estimates of these large-scale studies reflected the magnitude of the proportional effects of risk factors in the specific context of the Japanese population.

Our analysis had several limitations that should be noted. First, we focused on impacts of risk factors on mortality relative to changes in life expectancy and did not account for morbidity and disability. It is important in future studies to integrate these nonfatal health outcomes and examine disability-adjusted life years under the framework of comparative risk assessment in Japan. This is particularly true because the prognosis of non-communicable diseases has been improving with enhanced access to care, advances in medical technologies, and the standardization of treatment. Second, we could not incorporate standard metabolic equivalents in the categorization of exposures to physical inactivity because of the lack of detailed data from the 2007 survey, but instead we adopted a broader classification based on only the intensity and duration of physical activity that was used in the Global Burden of Disease Study in 2000. Third, data on dietary sodium intake until 1995 were recorded at the household level, which might increase uncertainty concerning the estimated stroke mortality attributable to high blood pressure in the early years. Fourth, we employed LDL cholesterol as an exposure metric for high concentrations of serum cholesterol, because it is the major atherogenic lipoprotein and a primary target for prevention of coronary heart disease [65]. It is, however, also a possibility for future studies to examine effects of low concentrations of high density lipoproteins, because growing evidence indicates that it plays an important role in atherogenesis [65]. Last, some of the Japanese population studies included in this analysis did not exclude disease end points occurring within a certain period after baseline in estimating relative risks. A few studies, however, conducted additional analyses and proved that changes in their results were minor.

To sustain the trend of longevity in Japan for the 21st century, additional efforts in a variety of fields are required for decreasing adult mortality from chronic diseases and injuries. A first step will be to powerfully promote effective programs for smoking cessation. Indeed, tobacco smoking is deeply rooted in Japanese society, and coordinating among interests of ministries and industries is hard. Health care professionals, including physicians, who are highly conscious of the harms of tobacco will play the primary role in treatment of smoking and creating an environment for implementation of stringent tobacco control policies. Moreover, it is urgent to establish a monitoring system for management of high blood pressure at the national level. Further investigation through national health surveys will help understand factors that contribute to the inadequate control of blood pressure in the Japanese population. Measuring the quality of the care that is actually delivered by interventions will be of paramount importance in the assessment of current policies and programs for the treatment of multiple cardiovascular risks including hypertension. These concerted actions in research, public health, clinical practice, and policymaking will be the key for maintaining good population health in the aging society.

Supporting Information

Alternative Language Article S1 Translation of the article into Japanese by the authors.
(DOCX)

Table S1 Relative risks for the effects of physiological risk factors on non-communicable diseases.
(DOCX)

Table S2 Relative risks for the effects of alcohol use on disease outcomes from meta-analyses.
(DOCX)

Table S3 Relative risks for the effects of alcohol use on disease outcomes from Japanese studies.
(DOCX)

Table S4 Relative risks for the effects of tobacco smoking on disease outcomes.

(DOCX)

Table S5 Relative risks for the effects of physical inactivity on disease outcomes.
(DOCX)

Table S6 Relative risks for the effects of dietary risk factors on disease outcomes.
(DOCX)

Table S7 Relative risks for the effects of infections on disease outcomes.
(DOCX)

Table S8 Population-attributable fractions of cause-specific mortality attributable to individual risk factors in men in 2007.
(DOCX)

Table S9 Population-attributable fractions of cause-specific mortality attributable to individual risk factors in women in 2007.
(DOCX)

Acknowledgments

We thank Goodarz Danaei, Hideki Hashimoto, Rintaro Mori, Christopher JL Murray, and Akira Oshima for their helpful comments; Amarjargal Dagvadorji, Farshad Farzadfar, Jinghua Li, and Mengru Wang for their technical assistance; Kazue Kondo, Ruriko Sano, Yasuko Sato, and Setsuko Shibuya for their administrative support.

Author Contributions

Conceived and designed the experiments: NI ME KS. Performed the experiments: NI KS. Analyzed the data: NI. Contributed reagents/materials/analysis tools: MN ME. Wrote the first draft of the manuscript: NI. Contributed to the writing of the manuscript: MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. ICMJE criteria for authorship read and met: NI MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. Agree with manuscript results and conclusions: NI MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. Supervised the research: KS. Literature search and data collection of exposures, relative risks and mortality: NI MI HIso MN TM HImano ES KK TSobue ST MN ME KS.

References

- World Health Organization (2011) Disease and injury regional estimates. Cause-specific mortality: regional estimates for 2008. Available: http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html. Accessed 20 December 2011.
- World Health Organization (2009) Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization.
- Ministry of Health, Labour and Welfare (2010) Abridged life tables for Japan 2009. Tokyo: Ministry of Health, Labour and Welfare.
- Ikeda N, Saito E, Kondo N, Inoue M, Ikeda S, et al. (2011) What has made the population of Japan healthy? *Lancet* 378: 1094–1105.
- Ministry of Health, Labour and Welfare (2011) Vital statistics. Available: <http://www.mhlw.go.jp/english/database/db-hw/index.html>. Accessed 5 July 2011.
- Ministry of Health, Labour and Welfare (2007) [Annual health, labour and welfare report 2007–2008.]. Tokyo: Ministry of Health, Labour and Welfare.
- Ministry of Health, Labour and Welfare (2011) [Final evaluation of Health Japan 21. October 13, 2011.] Available: <http://www.mhlw.go.jp/stf/houdou/2r9852000001r5gc.html>. Accessed 23 October 2011.
- Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, et al. (2009) Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). *Stroke* 40: 1571–1577.
- Inoue M, Nagata C, Tsuji I, Sugawara Y, Wakai K, et al. (2010) Impact of alcohol intake on total mortality and mortality from major causes in Japan: a pooled analysis of six large-scale cohort studies. *J Epidemiol Community Health*;E-pub ahead of print.
- Takashima N, Miura K, Hozawa A, Kadota A, Okamura T, et al. (2010) Population attributable fraction of smoking and metabolic syndrome on cardiovascular disease mortality in Japan: a 15-year follow up of NIPPON DATA90. *BMC Public Health* 10: 306.
- Murakami Y, Miura K, Okamura T, Ueshima H (2011) Population attributable numbers and fractions of deaths due to smoking: a pooled analysis of 180,000 Japanese. *Prev Med* 52: 60–65.
- Hozawa A, Okamura T, Murakami Y, Kadowaki T, Nakamura K, et al. (2007) Joint impact of smoking and hypertension on cardiovascular disease and all-cause mortality in Japan: NIPPON DATA80, a 19-year follow-up. *Hypertens Res* 30: 1169–1175.
- Hozawa A (2011) Attributable fractions of risk factors for cardiovascular diseases. *J Epidemiol* 21: 81–86.
- Ozasa K, Katanoda K, Tamakoshi A, Sato H, Tajima K, et al. (2008) Reduced life expectancy due to smoking in large-scale cohort studies in Japan. *J Epidemiol* 18: 111–118.
- Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, et al. (2008) Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *J Epidemiol* 18: 251–264.
- Murakami Y, Ueshima H, Okamura T, Kadowaki T, Hozawa A, et al. (2007) Life expectancy among Japanese of different smoking status in Japan: NIPPON DATA80. *J Epidemiol* 17: 31–37.
- Ezzati M, Vander Hoorn S, Lopez AD, Danaei G, Rodgers A, et al. (2006) Comparative quantification of mortality and burden of disease attributable to selected risk factors. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. *Global burden of disease and risk factors*. Oxford: Oxford University Press. pp 241–396.
- Murray C, Ezzati M, Lopez A, Rodgers A, Vander Hoorn S (2003) Comparative quantification of health risks: conceptual framework and methodological issues. *Popul Health Metr* 1: 1.
- Stevens G, Dias RH, Thomas KJ, Rivera JA, Carvalho N, et al. (2008) Characterizing the epidemiological transition in Mexico: national and subnational burden of diseases, injuries, and risk factors. *PLoS Med* 5: e125. doi:10.1371/journal.pmed.0050125.

20. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, et al. (2009) The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med* 6: e1000058. doi:10.1371/journal.pmed.1000058.
21. Danaei G, Rimm EB, Oza S, Kulkarni SC, Murray CJ, et al. (2010) The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med* 7: e1000248. doi:10.1371/journal.pmed.1000248.
22. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam J, Marcus J, et al. (2011) National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. *Popul Health Metr* 9: 55.
23. Ministry of Health, Labour and Welfare (2009) Vital statistics of Japan 2007. Tokyo: Ministry of Health, Labour and Welfare.
24. Institute for Health Metrics and Evaluation (2010) Institute for Health Metrics and Evaluation Database. Seattle (Washington): Institute for Health Metrics and Evaluation, University of Washington.
25. Naghavi M, Makela S, Foreman K, O'Brien J, Pourmalek F, et al. (2010) Algorithms for enhancing public health utility of national causes-of-death data. *Popul Health Metr* 8: 9.
26. Parkin DM (2006) The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030–3044.
27. Yoshizawa H (2002) Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 62(Suppl 1): 8–17.
28. Ministry of Health, Labour and Welfare (2010) The national health and nutrition survey in Japan, 2007. Tokyo: Ministry of Health, Labour and Welfare.
29. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus (2010) Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *Diabetol Int* 1: 2–20.
30. Ito C, Maeda R, Ishida S, Sasaki H, Harada H (2000) Correlation among fasting plasma glucose, two-hour plasma glucose levels in OGTT and HbA1c. *Diabetes Res Clin Pract* 50: 225–230.
31. Cabinet of Japan Food Safety Committee (2007) [Evaluative report on trans fatty acid content in foods: total confirmation assessment in 2006.]. Tokyo: Cabinet of Japan Food Safety Committee.
32. Willett W, Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 124: 17–27.
33. Peto R, Lopez AD, Boreham J, Thun M, Heath C, Jr. (1992) Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 339: 1268–1278.
34. Ezzati M, Henley SJ, Thun MJ, Lopez AD (2005) Role of smoking in global and regional cardiovascular mortality. *Circulation* 112: 489–497.
35. Wakai K, Marugame T, Kuriyama S, Sobue T, Tamakoshi A, et al. (2007) Decrease in risk of lung cancer death in Japanese men after smoking cessation by age at quitting: pooled analysis of three large-scale cohort studies. *Cancer Sci* 98: 584–589.
36. Sobue T (2008) [Research on collection of scientific evidence on tobacco smoking. Report to the Ministry of Health, Labour and Welfare for 2005–2007 Grants-in-Aid for Scientific Research.]. Tokyo: National Cancer Center.
37. Tanaka H, Hiyama T, Tsukuma H, Okubo Y, Yamano H, et al. (1994) Prevalence of second generation antibody to hepatitis C virus among voluntary blood donors in Osaka, Japan. *Cancer Causes Control* 5: 409–413.
38. Kato M, Asaka M, Shimizu Y, Nobuta A, Takeda H, et al. (2004) Relationship between *Helicobacter pylori* infection and the prevalence, site and histological type of gastric cancer. *Aliment Pharmacol Ther* 20: 85–89.
39. Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, et al. (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12–19.
40. Hitosugi M, Maegawa M, Kido M, Kurosu A, Nagai T, et al. (2007) Trends in fatal traffic accidents due to alcohol-impaired driving in Japan relative to breath alcohol levels of drivers. *Jpn J Occup Med Traumatol* 55: 74–79.
41. King G, Tomz M, Wittenberg J (2000) Making the most of statistical analyses: improving interpretation and presentation. *Am J Polit Sci* 44: 347–361.
42. Marugame T, Kamo K, Sobue T, Akiba S, Mizuno S, et al. (2006) Trends in smoking by birth cohorts born between 1900 and 1977 in Japan. *Prev Med* 42: 120–127.
43. Organisation for Economic Co-operation and Development (2011) OECD health data: non-medical determinants of health [database]. OECD Health Statistics; doi:10.1787/data-00546-en.
44. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, et al. (2011) National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 377: 557–567.
45. World Health Organization (2011) WHO report on the global tobacco epidemic, 2011: warning about the dangers of tobacco. Geneva: World Health Organization.
46. Ikeda N, Gakidou E, Hasegawa T, Murray CJ (2008) Understanding the decline of mean systolic blood pressure in Japan: an analysis of pooled data from the National Nutrition Survey, 1986–2002. *Bull World Health Organ* 86: 978–988.
47. Shimamoto T, Iso H, Iida M, Komachi Y (1996) Epidemiology of cerebrovascular disease: stroke epidemic in Japan. *J Epidemiol* 6: S43–S47.
48. Hashimoto H, Ikegami N, Shibuya K, Izumida N, Noguchi H, et al. (2011) Cost containment and quality of care in Japan: is there a trade-off? *Lancet* 378: 1174–1182.
49. Ohkubo T, Obara T, Funahashi J, Kikuya M, Asayama K, et al. (2004) Control of blood pressure as measured at home and office, and comparison with physicians' assessment of control among treated hypertensive patients in Japan: first report of the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) study. *Hypertens Res* 27: 755–763.
50. Kawabe H, Saito I, Saruta T (2005) Status of home blood pressure measured in morning and evening: evaluation in normotensives and hypertensives in Japanese urban population. *Hypertens Res* 28: 491–498.
51. Anderson CAM, Appel LJ, Okuda N, Brown IJ, Chan Q, et al. (2010) Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP Study. *J Am Diet Assoc* 110: 736–745.
52. World Health Organization (2007) Reducing salt intake in populations: report of a WHO forum and technical meeting, 5–7 October 2006, Paris, France. Geneva: World Health Organization.
53. Oghara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, et al. (2009) The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res* 32: 3–107.
54. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, et al. (2007) Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb* 14: 45–50.
55. NIPPON DATA Research Group (2006) Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J* 70: 1249–1255.
56. World Health Organization (2011) Noncommunicable diseases country profiles 2011. Geneva: World Health Organization.
57. World Health Organization (2010) Global recommendations on physical activity for health. Geneva: World Health Organization.
58. Akechi T, Iwasaki M, Uchitomi Y, Tsugane S (2006) Alcohol consumption and suicide among middle-aged men in Japan. *Br J Psychiatry* 188: 231–236.
59. National Police Agency of Japan (2011) Information on suicide in 2010. Available: <http://www.npa.go.jp/safetylife/seianki/H22jisatsunogaiyou.pdf>. Accessed 9 April 2011.
60. Yeh J, Goldie S, Kuntz K, Ezzati M (2009) Effects of *Helicobacter pylori* infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections. *Cancer Causes Control* 20: 2021–2029.
61. Tsukuma H, Tanaka H, Ajiki W, Oshima A (2005) Liver cancer and its prevention. *Asian Pac J Cancer Prev* 6: 244–250.
62. Shibuya K, Yano E (2005) Regression analysis of trends in mortality from hepatocellular carcinoma in Japan, 1972–2001. *Int J Epidemiol* 34: 397–402.
63. Olshansky S, Carnes B, Cassel C (1990) In search of Methuselah: estimating the upper limits to human longevity. *Science* 250: 634–640.
64. Wilmoth JR, Deegan LJ, Lundström H, Horiuchi S (2000) Increase of maximum life-span in Sweden, 1861–1999. *Science* 289: 2366–2368.
65. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106: 3143.
66. Japan Diabetes Society (2010) [Evidence-based guideline for diagnosis and treatment of diabetes 2010.]. Tokyo: Nankodo.
67. Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, et al. (1991) Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes* 15: 1–5.