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.
[a]A combination of high blood glucose, high LDL cholesterol, high blood pressure (directly, and indirectly through high dietary salt intake), and high body mass index.
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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

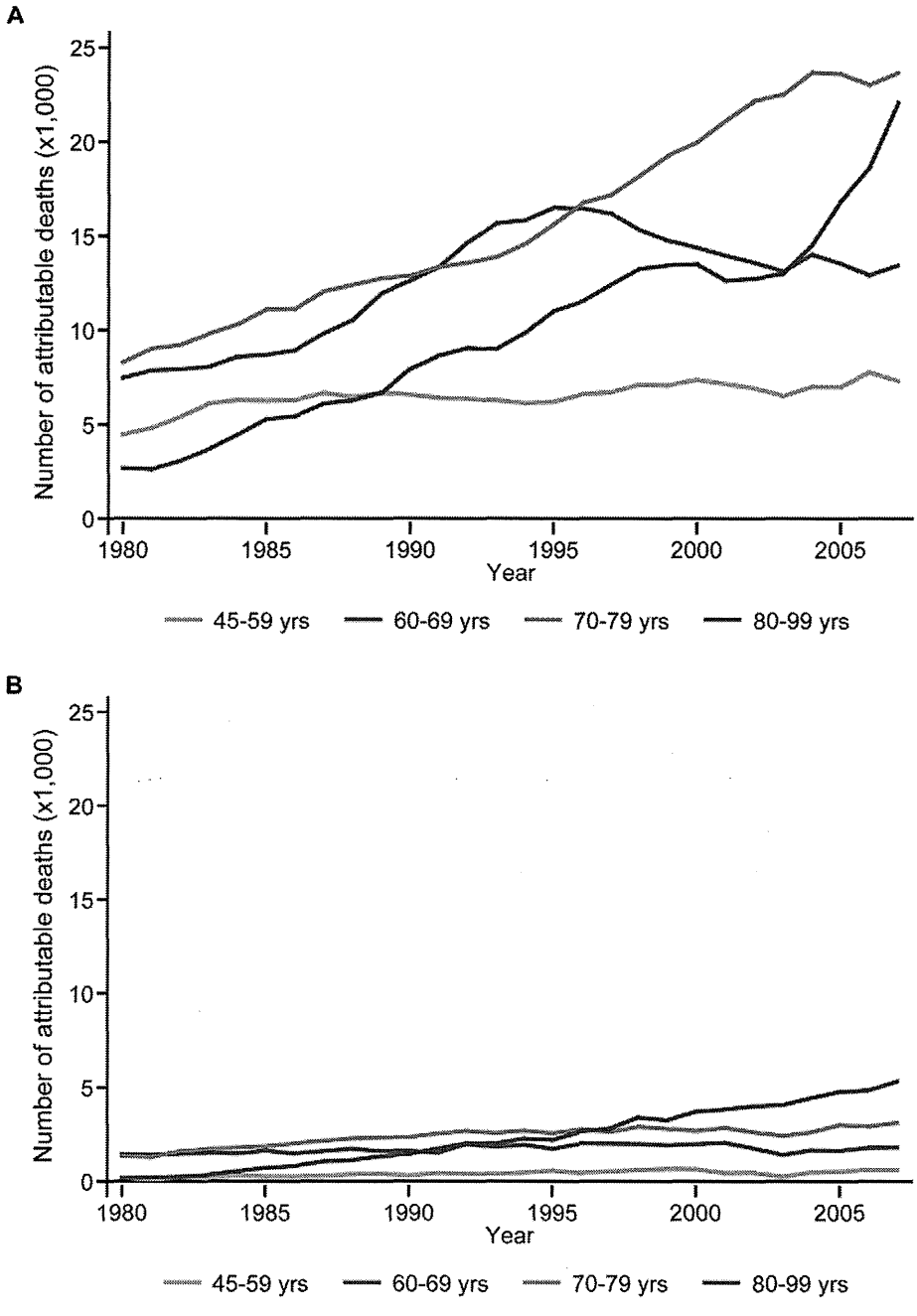

Figure 2. Cancer deaths attributable to tobacco smoking, by age group, 1980–2007. Data for (A) men and (B) women.
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purchasing tobacco products. Thus, the progress in tobacco control policies is slow, largely because Japanese society is relatively tolerant 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

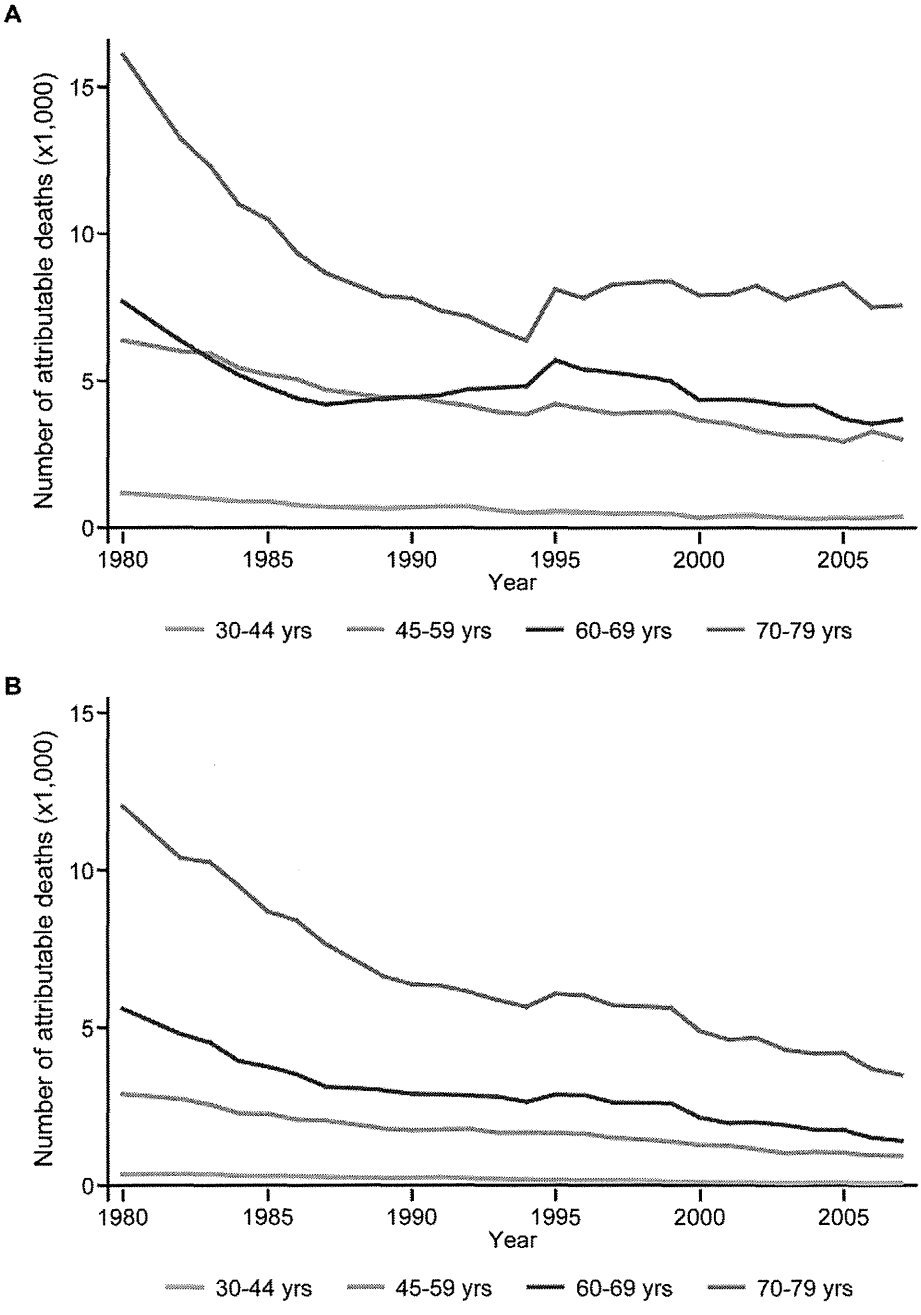

Figure 3. Stroke deaths attributable to high blood pressure, by age group, 1980–2007. Data for (A) men and (B) women.
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educational services for prevention of cardiovascular diseases [47].

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 unscreened 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)

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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

1. World Health Organization (2011) Disease and injury regional estimates. Cause-specific mortaliy: regional estimates for 2008. Available: http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html. Accessed 20 December 2011.
2. World Health Organization (2009) Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization.
3. Ministry of Health, Labour and Welfare (2010) Abridged life tables for Japan 2009. Tokyo: Ministry of Health, Labour and Welfare.
4. 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.
5. 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.
6. Ministry of Health, Labour and Welfare (2007) [Annual health, labour and welfare report 2007–2008.]. Tokyo: Ministry of Health, Labour and Welfare.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. Hozawa A (2011) Attributable fractions of risk factors for cardiovascular diseases. J Epidemiol 21: 81–86.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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. Ogihara 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.

Editors' Summary

Background. Worldwide, a small number of modifiable risk factors are responsible for many premature or preventable deaths. For example, having high blood pressure (hypertension) increases a person's risk of developing life-threatening heart problems and stroke (cardiovascular disease). Similarly, having a high blood sugar level increases the risk of developing diabetes, a chronic (long-term) disease that can lead to cardiovascular problems and kidney failure, and half of all long-term tobacco smokers in Western populations will die prematurely from diseases related to smoking, such as lung cancer. Importantly, the five major risk factors for death globally—high blood pressure, tobacco use, high blood sugar, physical inactivity, and overweight and obesity—are all modifiable. That is, lifestyle changes and dietary changes such as exercising more, reducing salt intake, and increasing fruit and vegetable intake can reduce an individual's exposure to these risk factors and one's chances of premature death. Moreover, public health programs designed to reduce a population's exposure to modifiable risk factors should reduce preventable deaths in that population.

Why Was This Study Done? In 2000, the Japanese government initiated Health Japan 21, a ten-year national health promotion campaign designed to prevent premature death from non-communicable (noninfectious) diseases and injuries. This campaign set 59 goals to monitor and improve risk factor management in the Japanese population, which has one of the longest life expectancies at birth in the world (the life expectancy of a person born in Japan in 2009 was 83.1 years). Because the campaign's final evaluation revealed deterioration or no improvement on some of these goals, the Japanese government recently released new guidelines that stress the importance of simultaneously controlling multiple risk factors for chronic diseases. However, although several studies have quantified the impacts on life expectancy and cause-specific death of individual modifiable risk factors in Japan, the effects of multiple risk factors have not been assessed. In this study, the researchers use a "comparative risk assessment" framework to estimate the effects of 16 risk factors on cause-specific deaths and life expectancy in Japan. Comparative risk assessment estimates the number of deaths that would be prevented if current distributions of risk factor exposures were changed to hypothetical optimal distributions.

What Did the Researchers Do and Find? The researchers obtained data on exposure to the selected risk factors from the 2007 Japanese National Health and Nutrition Survey and from epidemiological studies, and information on the number of deaths in 2007 from different diseases from official records. They used published studies to estimate how much each factor increases the risk of death from each disease and then used a mathematical formula to estimate the effects of the risk factors on the number of deaths in Japan and on life expectancy at age 40. In 2007, tobacco smoking and high blood pressure accounted for 129,000 and 104,000 deaths, respectively, in Japan. Physical inactivity accounted for 52,000 deaths, high blood glucose and high dietary salt intake accounted for 34,000 deaths each, and alcohol use for 31,000 deaths. Life expectancy at age 40 in 2007 would have been extended by 1.4 years for both sexes, the researchers estimate, if exposure to multiple cardiovascular risk factors had been reduced to calculated optimal distributions, or by 0.7 years if these risk factors had been reduced to the distributions defined by national guidelines and goals.

What Do These Findings Mean? These findings identify tobacco smoking and high blood pressure as the major risk factors for death from non-communicable diseases among adults in Japan, a result consistent with previous findings from the US. They also indicate that simultaneous control of multiple risk factors has great potential for producing health gains among the Japanese population. Although the researchers focused on estimating the effect of these risk factors on mortality and did not include illness and disability in this study, these findings nevertheless identify two areas of public health policy that need to be strengthened to improve health, reduce death rates, and increase life expectancy among the Japanese population. First, they highlight the need to reduce tobacco smoking, particularly among men. Second and most importantly, these findings emphasize the need to improve ongoing programs designed to help people manage multiple cardiovascular risk factors, including high blood pressure.

Additional Information. Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001160.

- The US Centers for Disease Control and Prevention provides information on all aspects of healthy living
- The *World Health Report 2002—Reducing Risks, Promoting Healthy Life* provides a global analysis of how healthy life expectancy could be increased
- The American Heart Association and the American Cancer Society provide information on many important risk factors for noncommunicable diseases and include some personal stories about keeping healthy
- Details about Health Japan 21 are provided by the Japanese Ministry of Health, Labour and Welfare. Further details about this campaign are available from the World Health Organization
- MedlinePlus provides links to further resources on healthy living and on healthy aging (in English and Spanish)

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Physical activity and risk of cognitive decline: a meta-analysis of prospective studies

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Abstract. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C (Centro S. Maria agli Ulivi, Onlus IRCCS; Thrombosis Centre, University of Florence; Azienda Ospedaliero-Universitaria Careggi, Florence, Italy). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2011; **269**: 107–117.

Objective. The relationship between physical activity and cognitive function is intriguing but controversial. We performed a systematic meta-analysis of all the available prospective studies that investigated the association between physical activity and risk of cognitive decline in nondemented subjects.

Methods. We conducted an electronic literature search through MedLine, Embase, Google Scholar, Web of Science, The Cochrane Library and bibliographies of retrieved articles up to January 2010. Studies were included if they analysed prospectively the association between physical activity and cognitive decline in nondemented subjects.

Results. After the review process, 15 prospective studies (12 cohorts) were included in the final analysis. These studies included 33 816 nondemented subjects followed for 1–12 years. A total of 3210 patients showed cognitive decline during the follow-up. The cumulative analysis for all the studies under a random-effects model showed that subjects who performed a high level of physical activity were significantly protected (–38%) against cognitive decline during the follow-up (hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.54–0.70; $P < 0.00001$). Furthermore, even analysis of low-to-moderate level exercise also showed a significant protection (–35%) against cognitive impairment (HR 0.65, 95% CI 0.57–0.75; $P < 0.00001$).

Conclusion. This is the first meta-analysis to evaluate the role of physical activity on cognitive decline amongst nondemented subjects. The present results suggest a significant and consistent protection for all levels of physical activity against the occurrence of cognitive decline.

Keywords: cognitive decline, dementia, exercise, physical activity.

Introduction

It is unquestionable that physical activity has positive effects on health; indeed, over the last few decades, a large body of evidence has shown that physical activity helps to reduce the risk of cardiovascular and cerebrovascular diseases, diabetes, obesity, hypertension and some cancers [1]. Moreover, it has been demonstrated that an active lifestyle impacts on all causes of mortality. With ageing, some cognitive functions such as attention, memory and concentration decline, becoming slower and inefficient, as for some physical functions such as walking and balance. These manifestations are the result of neural cell loss in the frontal, parietal and temporal lobes [2] and strongly depend on an ipofunction of the monoaminergic and cholinergic pathways [3]. Many of these cognitive changes are evident and can cause mild disability, even if a state of dementia is not reached.

Cognitve decline is heterogeneous, depending on various factors. Many studies have shown an inverse relation between physical activity and the risk of developing cognitive decline [4, 5], but the cause of the association has not been clearly established. Individuals who remain active throughout life, especially during middle age, generally have better cognitive

performance during later life, so preserving their cognitive functions for longer. Recent evidence suggests that in addition to reducing vascular risk factors, physical activity may increase directly the production of neurotrophic factors in the brain [6].

The results of a recent meta-analysis showed that physical exercise is able to reduce the incidence of neurodegenerative diseases; in particular, dementia and Alzheimer's disease [7]. By contrast, few and conflicting data are available on the possible protective role of physical activity on the occurrence of cognitive decline, independent of the onset of neurodegenerative disease [8–18].

Therefore, the aim of this study was to conduct a meta-analysis of all the available prospective cohort studies that investigated the association between physical activity and cognitive decline in nondemented subjects.

Methods

Selection of studies

Studies that investigated the possible association between physical activity and cognitive decline in nondemented adults were identified through a computerized search of all electronic databases: MedLine (source: *PubMed*, 1966 to January 2010), Embase (1980 to January 2010), Web of Science, The Cochrane Library (source: *The Cochrane Central Register of Controlled Trials*, 2009, issue 1), Clinicaltrials.org and Google Scholar. Relevant keywords relating to physical activity as Medical Subject Heading terms and text words ('*physical activity*' or '*physical exercise*' or '*exercise*', or '*fitness*' or '*training*') were used in combination with words relating to cognitive impairment ('*cognitive decline*' or '*cognitive function*', or '*cognitive impairment*' or '*cognitive loss*', or '*dementia*', or '*cognition*' or '*memory*'). We limited the search strategy to prospective cohort epidemiological studies, with no language restrictions, supplemented by manually reviewing the reference list of all retrieved articles.

Two investigators (FS, DV) assessed all potentially relevant articles for eligibility. The decision to include or exclude studies was hierarchical and made on the basis of the following: (i) the study title; (ii) the study abstract; and (iii) the complete study manuscript. In the event of conflicting opinions between investigators, disagreement was resolved through discussion.

Eligible studies were included if they met all of the following criteria: (i) a prospective cohort design; (ii) the association between physical activity and cognitive function as the primary or secondary outcome; (iii) nondemented subjects evaluated at baseline; (iv) clear definitions of methods used to assess cognitive performance and cognitive decline; (v) reported data on physical activity levels in relation to cognitive function; and (vi) reported estimates of association between physical activity and cognitive decline. Accordingly, studies were excluded if: (i) the design was cross-sectional, case control or interventional; (ii) outcomes other than those of interest for the meta-analysis were considered; (iii) patients with dementia or cognitive decline at baseline were included in the study; (iv) the association between physical activity and cognitive decline was not reported; or (v) estimates of the association between physical activity and the decline in cognitive function were not presented (Data S1).

The outcome of interest for the current meta-analysis was cognitive decline or cognitive impairment, defined as decline in cognitive functioning tests at follow-up examination (see Table 1 for further information about tests used to measure cognitive function).

Data extraction

All data were reviewed and separately extracted by two independent investigators (FS and DV) using a standardized form. The following patient characteristics were recorded: data and study cohort, country of the study cohort, baseline year, number of subjects at baseline, gender of the cohort, years of follow-up, age of the study cohort at baseline, definition of outcome of interest, methods used to assess cognitive function and physical activity, hazard ratio (HR) and confidence interval (CI) values for risk of cognitive decline, and adjustment for confounding factors in multivariate models.

Statistical analysis

We used Review Manager (RevMan; version 5.0.23 for Macintosh; Copenhagen, Denmark) to pool results from the individual studies.

Pooled results are reported as HR and are presented with 95% CI with two-sided *P* values using a random-effects model (DerSimonian and Laird method). $P < 0.05$ was considered to be statistically significant. When available, we used the results of the original studies from multivariate models with the most

Table 1 *Study characteristics*

Source, y *(Cohort)*	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, *(n) (Definition)*	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Ho *et al.*, 2001 [8]	China (1991)	519	M	3	≥70	Cognitive impairment (35) *(CAPE <8 points)*	Information/ orientation part of the Clifton Assessment Procedure for the elderly (CAPE)	Questionnaire (*Categories based on engagement in a not-otherwise specified exercise)*	No Yes	1.00 0.53 (0.25–1.11)	Age, education
Ho *et al.*, 2001 [8]	China (1991)	469	F	3	≥70	Cognitive impairment (104) *(CAPE <8 points)*	Information/ orientation part of the Clifton Assessment Procedure for the elderly (CAPE)	Questionnaire (*Categories based on engagement in a not-otherwise specified exercise)*	No Yes	1.00 0.53 (0.31–0.83)	Age, education
Laurin *et al.*, 2001 [9] *(Canadian Study of Health and Aging)*	Canada (1991)	1831	M	5	≥65	Cognitive impairment-No Dementia (179) *(According to WHO ICDs)*	MMSE and clinical evaluation	Questionnaire *(Categories based on frequency and intensity of exercises)*	None Low Moderate High	1.00 0.65 (0.30–1.38) 0.84 (0.53–1.34) 0.68 (0.39–1.20)	Age, education, smoking, alcohol, NSAIDs, functional ability in basic and DALYs, self-rated health, chronic conditions
Laurin *et al.*, 2001 [9] *(Canadian Study of Health and Aging)*	Canada (1991)	2784	F	5	≥65	Cognitive impairment-No Dementia (257) *(According to WHO ICDs)*	MMSE and clinical evaluation	Questionnaire *(Categories based on frequency and intensity of exercises)*	None Low Moderate High	1.00 0.69 (0.41–1.16) 0.55 (0.36–0.82) 0.47 (0.25–0.90)	Age, education, smoking, alcohol, NSAIDs, functional ability in basic and DALYs, self-rated health, chronic conditions

Table 1 (*Continued*)

Source, y (*Cohort*)	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) (*Definition*)	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Schuit *et al.*, 2001 [10] *(The Zutphen Elderly Study)*	The Netherlands (1990)	347	M	3	Mean: 74.6	Cognitive decline (47) *(≥3 decline on MMSE)*	MMSE	Questionnaire *(Frequency and duration of exercise and then converted in minutes/day)*	≤30 min day^{-1}31–60 min day^{-1} >60 min day^{-1}	1.00 0.56 (0.19–1.67) 0.50 (0.18–1.43)	Age, education, alcohol, smoking, cognitive function at baseline, disabilities ADL, self-reported health, history of MI, angina, TIA, diabetes, CVD
Yaffe *et al.*, 2001 [5] *(Study of Osteoporotic Fractures)*	US (1986)	5925	F	Mean: 7.5	≥65	Cognitive decline (1178) *(≥3-point decline on MMSE)*	MMSE	Questionnaire *(Quartiles based on frequency and duration of exercises converted into kilocalories expended per week)*	1st quartile 2nd quartile 3rd quartile 4th quartile	1.00 0.90 (0.74–1.09) 0.78 (0.64–0.96) 0.74 (0.60–0.90)	Age, education, health status, functional limitation, depression score, stroke, diabetes, hypertension, MI, smoking, oestrogen use
Pignatti *et al.*, 2002 [11]	Italy	1201	F	12	70–75	Cognitive decline (104) *(≥1-point decline on MSQ)*	MSQ	Questionnaire *(Categories based on type, frequency and intensity of exercises)*	Low High	1.00 0.27 (0.09–0.83)	MSQ at baseline
Lytle *et al.*, 2004 [12] *[Monongahela Valley Independent Elders Survey (MoVIES)]*	US (1987)	1146	M/F	2–4	≥65	Cognitive decline (110) *(≥3-point decline on MMSE)*	MMSE	Questionnaire *(Categories based on type, frequency and duration of exercises)*	None Low High	1.00 0.63 (0.39–0.99) 0.45 (0.22–0.95)	Age, gender, education, previous level of cognitive function, self-rated health status

Table 1 *(Continued)*

Source, y *(Cohort)*	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) *(Definition)*	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Flicker *et al.*, 2005 [13] *(Health in Men Study)*	Australia (1996)	618	M	Mean: 4.8	≥65	Cognitive Impairment (111) *(MMSE score <24 points)*	MMSE	Self-reported *(Categories based on frequency and intensity of exercises)*	Nonvigorous Vigorous	1.00 0.50 (0.25–0.99)	Age, education, treatment of hypertension, diabetes, consumption of full-cream milk, alcohol
Singh-Manoux *et al.*, 2005 [14] *(Whitehall II Study)*	UK (1985)	10 308	M/F	11	35–55	Cognitive function *(Lowest cognitive-functioning quintile)*	Cognitive test battery (20-word free-recall test of short-term memory; Alice-Heim 4-I test; Mill Hill Vocabulary Scale; Phonemic fluency; Semantic fluency) *(Alice-Heim 4-I test)*	Self-administered questionnaire *(Categories based on frequency and duration of exercises reported as hours per week)*	Low level Medium level High level	1.00 0.81 (0.65–1.02) 0.61 (0.48–0.78)	Age, gender, education, employment grade, self-rated health, blood pressure, cholesterol, smoking, mental health, social network index score, Mill Hill Vocabulary Scale
Sumic *et al.*, 2007 [15] *(The Oregon Brain Aging Study)*	US (1989)	39	M	Mean: 4.7	≥85	Cognitive Impairment (23) *(MMSE score <24 points)*	MMSE	Self-administered questionnaire *(Hours per week of exercises)*	≤4 h week^{-1} >4 h week^{-1}	1.00 0.91 (0.25–3.40)	Age, education, ApoE4, delayed recall test
Sumic *et al.*, 2007 [15] *(The Oregon Brain Aging Study)*	US (1989)	27	F	Mean: 4.7	≥85	Cognitive Impairment (15) *(MMSE score <24 points)*	MMSE	Self-administered questionnaire *(Hours per week of exercises)*	≤4 h week^{-1} >4 h week^{-1}	1.00 0.12 (0.03–0.41)	Age, education, ApoE4, delayed recall test

Table 1 (*Continued*)

Source, y (*Cohort*)	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) (*Definition*)	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Middleton *et al.*, 2008 [16] *(Canadian Study of Health and Aging)*	Canada (1991)	4683	M/F	5	≥65	Cognitive Impairment-No Dementia (454)	mMMSE	Self-administered questionnaire *(Categories based on frequency and intensity of exercises)*	Low Moderate-High	1.00 0.73 (0.59–0.91)	Age, gender, education, NSAIDs, vascular risk factor index
Niti *et al.*, 2008 [17] *(Singapore Longitudinal Aging Study)*	Singapore (2004)	1635	M/F	1–2	≥55	Cognitive decline (490) *(≥1-point decline on MMSE)*	MMSE	Questionnaire *(Categories based on frequency and intensity of exercises)*	Low Medium High	1.00 0.60 (0.45–0.79) 0.62 (0.46–0.84)	Age, gender, education, number of medical illness, hypertension, diabetes, cardiac diseases, stroke, smoking, alcohol, functional disability, depression, APOE-ε4 status, baseline MMSE
Etgen *et al.*, 2010 [18] *(The INVADE Study)*	Germany (2001)	3485	M/F	2	>55	Cognitive impairment (207) *(6CIT score >7)*	6CIT *(Short Blessed Test)*	Questionnaire *(Days per week of strenuous activities)*	No Moderate High	1.00 0.44 (0.24–0.83) 0.46 (0.25–0.85)	Age, gender, BMI, baseline 6CIT score, depression, alcohol, diabetes, IHD and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, smoking habit

CAPE, Clifton assessment procedure for the elderly; MMSE, mini-mental state examination; MSQ, mental status questionnaire; mMMSE, modified mini-mental state examination; APOE, apolipoprotein E; NSAIDs, nonsteroidal anti-inflammatory drugs; IHD, ischemic heart disease.

complete adjustment for potential confounders; the confounding variables included in this analysis are shown in Table 1.

The primary aim of the present meta-analysis was to evaluate whether high levels of physical activity were associated with significant protection against cognitive decline at follow-up. Thus, for studies reporting low levels of physical activity, instead of high, in relation to cognitive decline, we recalculated the HR using conventional procedures. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results. The I^2 value provides an estimate of the amount of variance across studies because of the heterogeneity rather than chance. Where I^2 was greater than 50%, heterogeneity was considered to be high. Moreover, to further investigate the heterogeneity across studies, we performed sensitivity analyses by dividing studies into groups according to their main characteristics. Subgroup analyses were then performed according to gender, mean sample size of the study populations (less than/at least 3500), mean duration of follow-up (less than/at least 5 years) and method used to evaluate cognitive function (mini-mental state examination (MMSE)/other). Publication bias was appraised by visual inspection of the funnel plot of effect size against standard error and, analytically, by the Egger's test.

Results

Study identification and selection

Our search strategy yielded 58 articles (Fig. 1). Of these, we first excluded 17 articles because they had a cross-sectional, case–control or interventional design. The selected articles were then carefully reviewed, and a further 14 articles were excluded because the reported outcome was incidence of dementia or Alzheimer's disease, i.e. not the outcome of interest. Subsequently, 12 papers were excluded because they did not report estimates of the association between physical activity and decline in cognitive function. The reasons for exclusion in all cases are reported as supplementary information.

Thus, 15 prospective studies [5, 8–18] were included in the analysis. Of these, three conducted analyses separately for men and women and so were entered into the final analysis each as a single paper. The number of participants included in the studies varied from 27 to 10 308, with a follow-up time ranging from 1 to 12 years. A total of 33 816 nondemented sub-

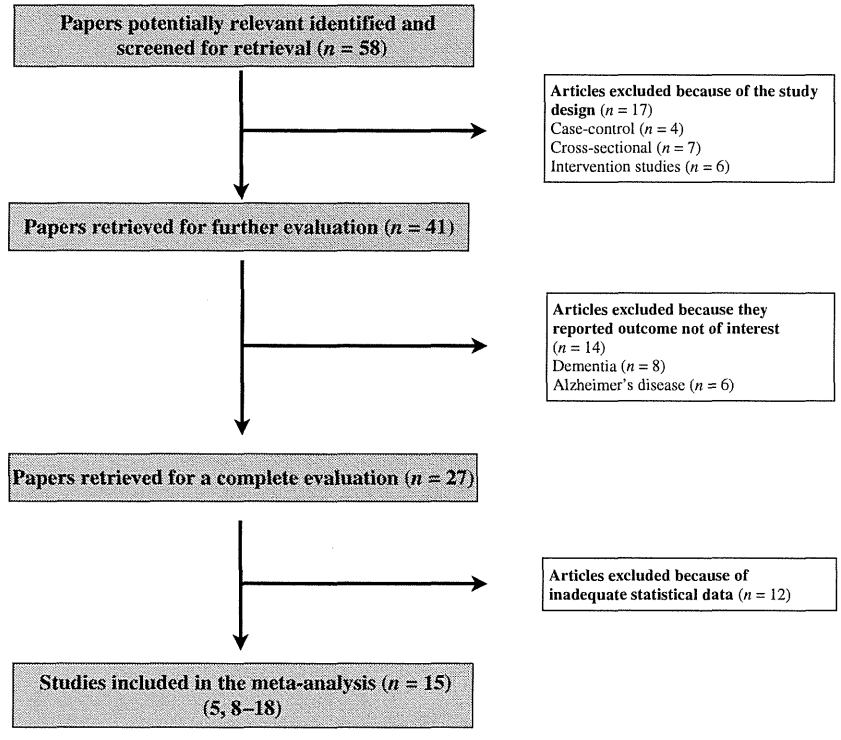

Fig. 1 *Flow chart of search strategy.*

jects were included in the analysis. During the follow-up period, 3210 incident cases of cognitive decline were reported.

Characteristics of the studies included in the meta-analysis are summarized in Table 1. The included studies were conducted all over the world, including China, Singapore, USA, Canada and Europe. All of the studies included only elderly subjects (>65 years) with the exception of the study by Singh-Manoux *et al.*, [14] that investigated younger subjects too. With regard to the methods used to assess cognitive functioning at baseline, most of the studies used the MMSE. In addition, the definition of cognitive decline at follow-up varied substantially in terms of points of decline for cognitive tests used to measure cognitive function.

Meta-analysis

Meta-analytic pooling under a random-effects model showed that subjects who performed physical activity at baseline had a significantly reduced risk of cognitive decline during follow-up. Indeed, by grouping studies according to the different levels of physical activity, subjects who reported performing a high level of activity had a 38% reduced risk of cognitive decline with respect to those who reported being sedentary (HR 0.62, 95% CI 0.54–0.70; $P < 0.00001$) (Fig. 2). We found no significant heterogeneity amongst the studies ($I^2 = 17\%$; $P = 0.26$).

Similarly, when low-to-moderate levels of physical activity were taken into consideration, the significant protection against cognitive decline during follow-up was still observed (HR 0.65, 95% CI 0.57–0.75; $P < 0.00001$), and with no significant heterogeneity amongst the studies ($I^2 = 33\%$; $P = 0.10$) (Fig. 3).

Sensitivity analyses

To investigate the possible differences across studies, we performed sensitivity analyses by grouping studies according to various characteristics such as gender of the study population, study size (mean size of the study sample was 3500), length of follow-up (mean duration was 5 years) and method used to determine cognitive function (MMSE/other). Smaller studies, including only women, and with a shorter duration of follow-up, showed a tendency towards a higher estimate of association in terms of significant reduced risk of cognitive decline, compared with larger studies, in men, and with a longer follow-up period (Table 2).

Publication bias

Funnel plots of effect size versus standard error to investigate possible publication bias were broadly symmetrical, suggesting the absence of publication bias for both high and moderate levels of physical activity ($P > 0.05$ for both levels, Egger's test) (Figs 4 and 5).

Discussion

This is the first meta-analysis that aimed to investigate the association between physical activity and cognitive decline in nondemented subjects. The overall analysis of 15 cohort prospective studies investigating 30 331 nondemented subjects followed for a period of 1–12 years and 3003 incident cases of cognitive decline showed that physically active individuals at baseline have a significantly reduced risk of developing cognitive decline during follow-up. Indeed, the cumulative analysis demonstrated a 38% reduced risk of cognitive decline in subjects with high

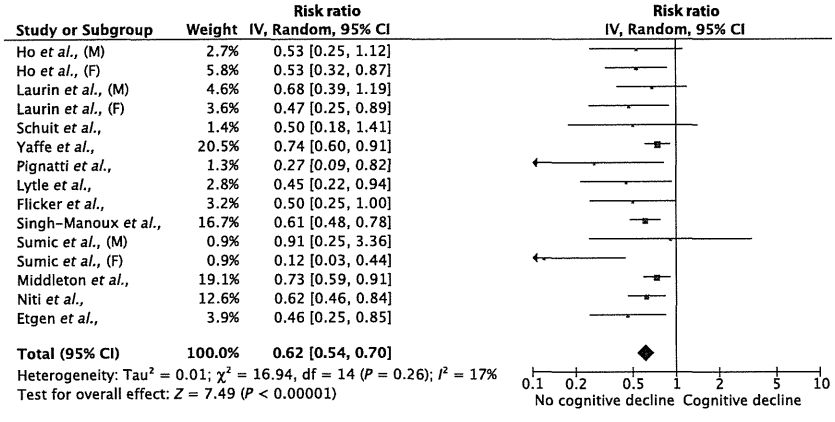

Fig. 2 *Forest plot of studies investigating a high level of physical activity.*

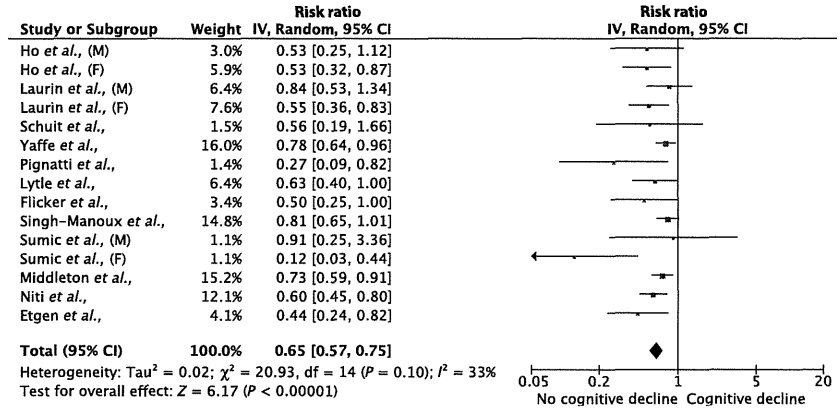

Fig. 3 *Forest plot of studies investigating a low-to-moderate level of physical activity.*

Table 2 *Subgroup analyses*

	Studies, *n*	High level of physical activity	Moderate level of physical activity
Gender			
Males	10	0.63 (0.56–0.72)	0.70 (0.62–0.79)
Females	10	0.60 (0.51–0.71)	0.63 (0.54–0.75)
Sample size			
<3500 subjects	12	0.53 (0.45–0.64)	0.57 (0.48–0.67)
≥3500 subjects	3	0.70 (0.62–0.79)	0.77 (0.68–0.87)
Duration of follow-up			
<5 years	9	0.54 (0.44–0.65)	0.55 (0.46–0.66)
≥5 years	6	0.67 (0.59–0.77)	0.74 (0.65–0.85)
Method used to determine cognitive function			
MMSE	10	0.64 (0.54–0.75)	0.67 (0.57–0.78)
Others	5	0.56 (0.46–0.68)	0.57 (0.50–0.80)

MMSE, mini-mental state examination.

levels of physical exercise, compared to sedentary subjects. Moreover, low-to-moderate levels of physical activity similarly resulted in a significantly reduced risk of deterioration of cognitive performance (–35%).

To date, few studies have investigated the relationship between an active lifestyle and cognitive performance in mentally healthy subjects, and results have been conflicting [8–18]. Recent data, including some from longitudinal studies and randomized trials, reported a significant association between physical activity during leisure time and a reduced risk of cognitive impairment at follow-up [4, 9], whereas other studies reported no significant benefit of physical activity on the decline in cognitive function [10, 19]. Recently, Hamer & Chida [7] conducted a meta-analysis to investigate the role of physical activity on the occurrence of neurodegenerative diseases in nondemented subjects. In the overall analysis, they found that physical activity is able to decrease the risk of neurodegenerative diseases such as clinical dementia and Alzheimer's disease, but they did not take into account cognitive decline as a clinical outcome. By contrast, the present meta-analysis is the first, to the best of our knowledge, that included only cognitive decline as the clinical outcome. The choice to study healthy subjects in relation to the decline in cognitive functions was based on the hypothesis that physical activity may help cognitive performance during ageing, by preventing disability rather than a specific disease. Cognitive decline can, in fact, occur as a part of the ageing processes of the brain, without leading to dementia but resulting in a poorer quality of life. Nonetheless, the diagnosis of dementia is based on a number of parameters other than the worsening of

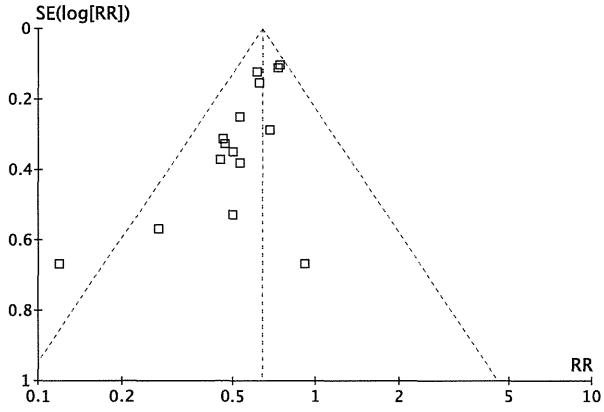

Fig. 4 *Funnel plot for studies investigating a high level of physical activity.*

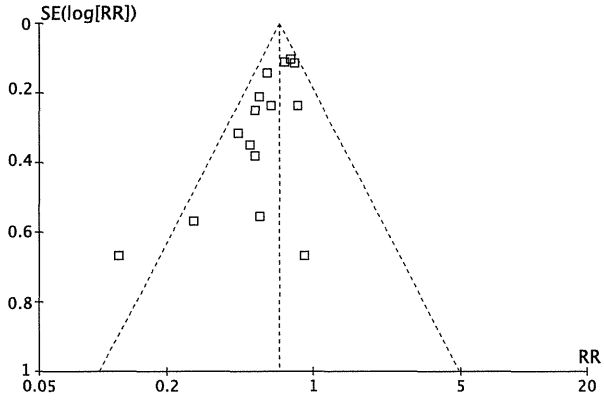

Fig. 5 *Funnel plot for studies investigating a low-to-moderate level of physical activity.*

cognitive performance, and patients referred to as 'nondemented' could show signs of slight cognitive decline as early clinical manifestations of neurodegenerative disease.

Several explanations for the protective effect of physical activity on cognitive functions have been suggested. First, physical exercise helps to maintain cerebrovascular integrity, by sustaining blood flow and the supply of oxygen and nutrients to the brain [20]. Furthermore, physical activity positively influences cardiovascular risk factors, such as diabetes, hypertension, obesity and dyslipidaemia, and reduces the incidence of cardiovascular and cerebrovascular events, with global haemodynamic benefits [21]. Secondly, another possible protective mechanism is the neurotrophic effect of physical exercise. This may stimulate the release of neurotrophins, increasing synapses and dendritic receptors, and promoting neuronal growth and survival [22]. Finally, it has been reported that an active lifestyle is able to prevent stress by reducing cortisol levels, which can positively influence cognitive function [23].

There are a few limitations in this meta-analysis. First, the methods used to investigate cognitive decline and levels of physical activity varied substantially across the included studies. The MMSE test was the most frequently used tool for the diagnosis of cognitive decline, but other tests were used in some studies. This might have resulted in a nonhomogenous definition of cognitive decline amongst the studies. Indeed, the MMSE test with the classical cut-off (>3-point decline at follow-up or a score lower than 24 points) seems to be very suitable for the diagnosis of cognitive decline but is affected by learning bias and is therefore less accurate compared to other neuropsychological tests. By contrast, however, sensitivity analysis showed no significant difference for estimates of association in relation to the different methods used to determine cognitive function. Moreover, with regard to physical activity, data were obtained from questionnaires; thus, bias could be introduced by misinterpretation of the questions and the personal perception of fatigue. In addition, studies differ in the methods used to classify the level of activity, ranging from studies with a simple differentiation of active/not active to others with three or four levels of intensity. Nevertheless, heterogeneity results as well as subgroup analyses did not show any significant differences in risk reduction amongst physically active subjects in terms of the intensity of activity. Indeed, in the overall results, we did not observe a dose–response effect; instead, we found similar estimates of association for both high and low-to-moderate intensity of exercise.

In conclusion, these results highlight the important role of physical activity in the protection of mental functions even in subjects without neurodegenerative disease. These considerations could be important especially because the population is ageing and a good cognitive function is fundamental for individual autonomy and quality of life, even in nondemented subjects. The effect of physical activity does not appear to be dose dependent, but may be stronger in women than in men. However, further studies are needed to determine the optimal type, frequency and intensity of exercise to preserve the integrity of cognitive function.

Conflict of interest statement

No conflict of interest was declared.

References

1 A guide for population-based approaches to increasing levels of physical activity. Implementation of the WHO global strategy on diet, physical activity, and health. Geneva, Switzerland: World Health Organization, 2007 (Available at http://www.who.int/dietphysicalactivity/pa/en/index.html).

2 Jernigan TL, Archibald SL, Fennema-Notestine C *et al.* Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging* 2001; **22:** 581–94.

3 Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci* 2004; **5:** 483–94.

4 Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 2004; **292:** 1454–561.

5 Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med* 2001; **161:** 1703–8.

6 Dishman RK, Berthoud HR, Booth FW *et al.* Neurobiology of exercise. *Obesity* 2006; **14:** 345–56.

7 Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective studies. *Psychol Med* 2009; **39:** 3–11.

8 Ho SC, Woo J, Sham A, Chan SG, Yu AL. A 3-year follow-up study of social, lifestyle and health predictors of cognitive impairment in a Chinese older cohort. *Int J Epidemiol* 2001; **30:** 1389–96.

9 Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001; **58:** 498–504.

10 Schuit AJ, Feskens EJ, Launer LJ, Kromhout D. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. *Med Sci Sports Exerc* 2001; **33:** 772–7.

11 Pignatti F, Rozzini R, Trabucchi M. Physical activity and cognitive decline in elderly persons. *Arch Intern Med* 2002; **162:** 361–2.

12 Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline: the MoVIES project. *Alzheimer Dis Assoc Disord* 2004; **18:** 57–64.

13 Flicker L, Almeida OP, Acres J *et al.* Predictors of impaired cognitive function in men over the age of 80 years: results from the Health in Men Study. *Age Ageing* 2005; **34:** 77–80.

14 Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. *Am J Public Health* 2005; **95:** 2252–8.

15 Sumic A, Michael YL, Carlson NE, Howieson DB, Kaye JA. Physical activity and the risk of dementia in oldest old. *J Aging Health* 2007; **19:** 242–59.

16 Middleton L, Kirkland S, Rockwood K. Prevention of CIND by physical activity: different impact on VCI-ND compared with MCI. *J Neurol Sci* 2008; **269:** 80–4.

17 Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. *Int Psychogeriatr* 2008; **20:** 237–51.

18 Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons. The INVADE study. *Arch Intern Med* 2010; **170:** 186–93.

19 Madden DJ, Blumenthal JA, Allen PA, Emery CF. Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychol Aging* 1989; **4:** 307–20.

20 Chodzko-Zajko WJ, Moore KA. Physical fitness and cognitive functioning in aging. *Exerc Sport Sci Rev* 1994; **22:** 195–220.

21 Sofi F, Capalbo A, Marcucci R *et al.* Leisure time but not occupational physical activity significantly affects cardiovascular risk factors in an adult population. *Eur J Clin Invest* 2007; **37:** 947–53.

22 Gomez-Pinilla F, So V, Kesslak JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. *Neuroscience* 1998; **85:** 53–61.

23 Kalmijn S, Launer LJ, Stolk RP *et al.* A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *J Clin Endocrinol Metab* 1998; **83:** 3487–92.

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Data S1. Reasons of exclusion.

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Methods for Trend Estimation from Summarized Dose-Response Data, with Applications to Meta-Analysis

Sander Greenland and Matthew P. Longnecker

Meta-analysis often requires pooling of correlated estimates to compute regression slopes (trends) across different exposure or treatment levels. The authors propose two methods that account for the correlations but require only the summary estimates and marginal data from the studies. These methods provide more efficient estimates of regression slope, more accurate variance estimates, and more valid heterogeneity tests than those previously available. One method also allows estimation of nonlinear trend components, such as quadratic effects. The authors illustrate these methods in a meta-analysis of alcohol use and breast cancer. *Am J Epidemiol* 1992;135:1301–9.

epidemiologic methods; logistic models; meta-analysis; risk assessment

Meta-analytic methods for clinical trial data often assume that sufficient data are available from each study to allow use of ordinary analytic methods. Nevertheless, meta-analyses of observational studies often have to rely on the limited data available from research reports, and they may have to reconstruct the more complete data required for regression analysis (1).

To obtain a regression slope from a research report, one may have to pool estimates for responses at different levels of exposure or treatment. Current methods for pooling estimates assume independence of the estimates, an assumption that is never true because the estimates for separate exposure levels depend on the same reference (unexposed) group. We present two new methods of pooling that account for the correlation between estimates, and we compare the results of applying these methods with the results from methods that assume independence.

TREND ESTIMATION FROM A SINGLE REPORT

As a motivating example, consider the case-control data in table 1 on alcohol and breast cancer, first presented by Rohan and McMichael (2). From these data, we wish to estimate the coefficient β in the logit-linear (linear-logistic) model

$$\lambda(x, z) = \alpha + \beta x + \boldsymbol{\delta}'\mathbf{z},$$

where x is alcohol intake, $\mathbf{z}$ is the vector of covariates, and λ is the log odds of being a case in the study versus being a control. We do not have access to the original data, nor did the published article present enough data to allow us to fit the model to the data. Nevertheless, we can construct an estimate of β by using weighted least squares to regress the adjusted log

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TABLE 1. Case-control data on alcohol use and breast cancer, as presented by Rohan and McMichael (2)

Alcohol (g/day)	Assigned dose (g/day)	No. of cases	No. of controls	Total	Crude OR*	Adjusted OR†
0	0	165	172	337	1.0	1.0‡
<2.5	2	74	93	167	0.83	0.80 (0.51–1.27)§
2.5–9.3	6	90	96	186	0.98	1.16 (0.73–1.85)
>9.3	11	122	90	212	1.41	1.57 (0.99–2.51)
Total		451	451	902		

* OR, odds ratio.

† Odds ratio from age-matched conditional logistic regression including variables for history of benign breast disease, bilateral oophorectomy, smoking, education, family history of breast cancer, ages at first and last menstrual period, age at first live birth, ever use of oral contraceptives, ever use of replacement estrogens, and practice of breast self-examination.

‡ Referent.

§ Numbers in parentheses, 95% confidence interval.

odds ratios from table 1 on the exposure doses listed in column 1 of the table (1). Doing so yields an estimated β of $b = 0.0334$, with an estimated variance for b of $v = 0.0003494$.

Given the logistic model, the estimator b of β obtained using the preceding method is consistent for β. Nevertheless, b is inefficient; worse, the variance estimate v obtained from this regression underestimates the true variance of b (see Appendix 1). In effect, the variance estimator for b assumes that the log odds ratios are uncorrelated, an assumption that is never satisfied in practice and is often grossly violated. We have therefore developed a new approach that yields an efficient point estimator and a consistent variance estimator under assumptions more likely to be approximated in practice. Our approach is based on constructing an approximate covariance estimate for the adjusted log odds ratios from a fitted table that conforms to the adjusted log odds ratios.

For case-control and cumulative cohort data, our estimates are computed as follows:

1) Let the reference exposure level be coded zero;
   N_x = the total number of subjects at exposure level x;
   $\mathbf{N}$ = the vector of N_x;
   M_1 = the total number of cases;
   L_x = the adjusted log odds ratio estimate for exposure level x ($x \neq 0$) versus the reference level ($x = 0$);
   $\mathbf{L}$ = the vector of L_x ($x \neq 0$);
   v_x = the estimated variance for L_x (see Greenland (1) for methods of computing v_x from published reports);
   $\mathbf{v}$ = the vector of v_x ($x \neq 0$).
2) Fit cell counts to the interior of the total data table (which has margins N_x and M_1) such that $A_xB_0/(A_0B_x) = \exp(L_x)$, where A_x and $B_x = N_x - A_x$ are the fitted numbers of cases and noncases at exposure level x. (See Appendix 2 for a simple fitting algorithm.)
3) For $x \neq z$, estimate the asymptotic correlation of L_x and L_z by

$$r_{xz} = (1/A_0 + 1/B_0)/s_x s_z,$$

   where s_x^2 = crude variance estimate $= 1/A_x + 1/B_x + 1/A_0 + 1/B_0$.
4) Estimate the asymptotic covariance of L_x, L_z by

$$c_{xz} = r_{xz}(v_x v_z)^{1/2}.$$