Introduction

Osteoarthritis (OA) is an increasingly important public-health problem [1]. The total societal cost of the treatment of OA has been estimated to increase worldwide because of its dramatic growth in morbidity [2]. The current treatment for knee OA consists of conservative treatment, such as exercise, physical therapy, pharmacological agents and, in some cases, surgical treatment [3,4]. While many of the commonly used conservative treatments have been recognized to be effective [5], there is still insufficient evidence available.

Among the pharmacological treatments for knee OA, oral non-steroidal anti-inflammatory drugs (NSAIDs) act rapidly and are recommended for the management of OA, although frequent and serious adverse effects of NSAIDs have been recognized [5]. Hyaluronic acid (HA) is a natural constituent of joint fluid. Intra-articular injections of HA (IA-HA) for the treatment of knee OA have been shown to reduce the pain and improve joint function [5-7]. Although IA-HA is also recommended, it acts relatively slowly and there was considerable heterogeneity in the outcomes between trials [8-11]. In addition, there has been no qualified direct comparison study of efficacy and safety between IA-HA and NSAIDs for patients with knee OA.

The aim of this multicenter, randomized, parallel-group, open-label, non-inferiority trial was to compare the early efficacy and safety of IA-HA and NSAIDs in patients with knee OA.

Methods

Study design and participants

The trial was planned by the Cartilage Metabolism Research Group, consisting mainly of Japanese orthopedists, to clarify the early efficacy and safety of IA-HA (high molecular weight 2,700 kDa HA, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) in comparison to an NSAID (loxoprofen sodium, Daiichi Sankyo Pharmaceuticals Co. Ltd., Tokyo, Japan), in a multicenter, randomized, open-label, parallel-group, non-inferiority trial. The protocol was reviewed and approved by the ethics committee of Juntendo University, Tokyo, Japan, and was also reviewed by the institutional review board of each participating institution. This study was undertaken at 20 hospitals throughout Japan between February, 2008 and December, 2010 (see Acknowledgements), in accordance with the Declaration of Helsinki, and with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. This trial was registered at UMIN-CTR [12], UMIN000001026.

Subjects

All patients provided written informed consent before enrollment in this trial. The inclusion criteria for the present study included (1) subjects who were able to walk with painful knee OA and fulfilled the criteria for knee OA of the medial femorotibial joint as defined by the American College of Rheumatology (ACR) [13], (2) the age of the subjects ranged from 50 to 80, (3) female subjects were required to be postmenopausal, and (4) all subjects had radiographic knee OA with Kellgren-Lawrence (K/L) grade 1 to 3 [14] evaluated by the weight-bearing anteroposterior X-rays of the tibiofemoral joint using the bilateral standing extended view.

The exclusion criteria included (1) patients who had received either an oral, topical or intra-articular steroid during the four weeks before the study, (2) patients who had received IA-HA within four weeks before the study, (3) patients who had received either an oral, topical or suppository NSAID within two weeks before the study, (4) patients who had secondary knee OA, (5) patients with patellofemoral OA with a K/L grade of 3 or higher, (6) patients with severe OA (K/L grade 3 or higher) in a location other than the knee joint, (7) patients with rheumatoid arthritis, (8) patients who had received joint replacement surgery in either knee or/and a hip, (9) patients who had allergies to either HA or NSAIDs, (10) patients who had either hematological, cardiac, hepatic or renal disorders, (11) patients who had experienced an asthma attack induced by NSAIDs, and (12) patients whom the physician recognized as not suitable for enrollment in the study for other reasons.

Randomization and masking

A centralized, computer-generated randomization was conducted to randomly assign patients in a 1:1 ratio to the IA-HA or NSAID groups. Investigators were masked to assignment before, but not after, randomization. The website for patient registration and randomization was prepared and controlled by the coordinating data center (Gunma University, Maebashi, Japan). The blocked randomization was stratified by the participating medical center and the K/L grade of knee OA.

Treatment procedures

A total of 200 patients with symptomatic knee OA were registered from 20 hospitals and randomized for treatment with the NSAID or IA-HA, as described above. For patients treated with the NSAID, they received three daily 60 mg NSAID tablets (total 180 mg)/day, one after each meal, for five weeks. Additional use of gastro-protective drugs, such as a proton pump inhibitor (PPI), in combination with the NSAID was allowed for those in the NSAID group. For patients treated with IA-HA, an intra-articular injection of high-molecular-weight 2,700 kDa HA (25 mg) was administered into the affected joint five times, at weekly intervals in the morning. Concomitant use of other drugs for the treatment of OA and drugs that affect bone and cartilage metabolism were not allowed during the trial.

Outcome measures for the assessment of efficacy and safety

The patients were evaluated for their (1) baseline characteristics, (2) radiographic analysis of the knee, (3) compliance with the treatment, (4) clinical manifestations, and (5) safety.

Evaluation of the response to treatment (efficacy)

Pain was evaluated by a visual analog scale (VAS, 0 to 100). The clinical manifestations were evaluated by the Japanese Knee Osteoarthritis Measure (JKOM) score [15]. The JKOM is a patient-based, self-answered evaluation score that includes four subcategories: pain and stiffness (0 to 32), activities of daily living (0 to 40), social activities (0 to 20), and general health conditions (0 to 8) with 100 points as the maximum score. The JKOM score is higher in patients with more pain and physical disability, and this evaluation modality is considered to have sufficient reliability and validity for studies of the clinical outcomes of Japanese subjects with knee OA [15]. The measure has also been shown to have reliability and validity by means of statistical evaluation and comparison with other health-related scales, such as the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [15].

The primary endpoint was to compare the percentage change from baseline in the JKOM score at five weeks. The secondary endpoint was to compare the percentage change from baseline in the pain VAS score.

The definition of a response to treatment was made following the criteria defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI) [16]. This measure consists of both absolute and relative changes in scales, including both pain and function, to evaluate the affected knee. Relative change means the percentage of change during the study (final minus baseline over baseline × 100), whereas absolute change indicates the absolute change during the study (final minus baseline on an interval scale of 0 to 100). Before assessing patients based on this scale, we partly modified it for this study by using the JKOM score, as already reported [17,18]. The response was defined as relief of joint pain or improvement in function (at least 50% reduction of the score) and a decrease of at least 20 mm on the VAS, or clinical improvement meeting at least two of the following three conditions: a decrease in joint pain of at least 20% and at least 10 mm on the VAS; an improvement in function of at least 20% and a decrease of at least 4 points from a total 40 points (equal to an absolute change of 10%) on the JKOM functional subcategory scale; and a decrease in the patient's global assessment score by at least 20% and at least 10 points from a total of 100 on the total JKOM scale.

Assessment of adverse events induced according to the treatment modality (safety)

Safety was monitored by recording all adverse events, evaluating the laboratory data and assessing vital signs. This was performed for all participants in both groups at each weekly visit.

Statistical analysis

Sample size determination

The trial was designed to establish whether the symptom-modified effect of IA-HA was non-inferior to that of NSAID (Δ10%). The sample size of this non-inferiority trial was calculated to require a total of 194 patients (97 per treatment group) based on the results of our pilot study with a 5% dropout rate, 10% non-inferiority margin, 27% standard deviation (SD), 5% one-sided alpha level, and power = 0.8 (pilot study: Toshitaka Nakamura, unpublished data, 2007). The 10% margin was set as the smallest value that would be clinically important, assuming a reduction of 30% in the mean percentage change of JKOM score in patients with both IA-HA and NSAID treatment and a reduction of 10% those receiving a placebo treatment.

Data analysis

The primary statistical analyses of efficacy and safety were performed on the full analysis set (FAS), which included all patients treated at least once. For the primary endpoint of the study, a two-sided 95% confidence interval (CI) for the group difference 'test treatment minus reference treatment' was calculated for the percentage change from baseline in the JKOM score as non-inferiority analysis. The non-inferiority of the test treatment was confirmed if the upper limit of the CI was ≤ margin of non-inferiority delta (10%). For the secondary endpoint, the group difference and its 95% CI was calculated for the percentage change from baseline in the VAS pain score.

Quantitative variables were described using the mean, standard deviation and range. The efficacy of treatment was examined by a paired t test for both JKOM score and pain VAS score. A multiple logistic regression analysis was used to estimate odds ratios and their 95% CIs between the IA-HA and NSAID treatments in models adjusted for age, K/L grade, body mass index (BMI) and the participating medical centers.

All analyses were performed using the SAS System Release 9.1 software program (SAS Institute, Cary, NC, USA). The registration number of this trial is UMIN000001026, and information on the trial can be found online at [12].

Results

Patient baseline characteristics

A flow chart of this trial is shown in Figure 1. When 200 patients were enrolled, half (100) of the patients were

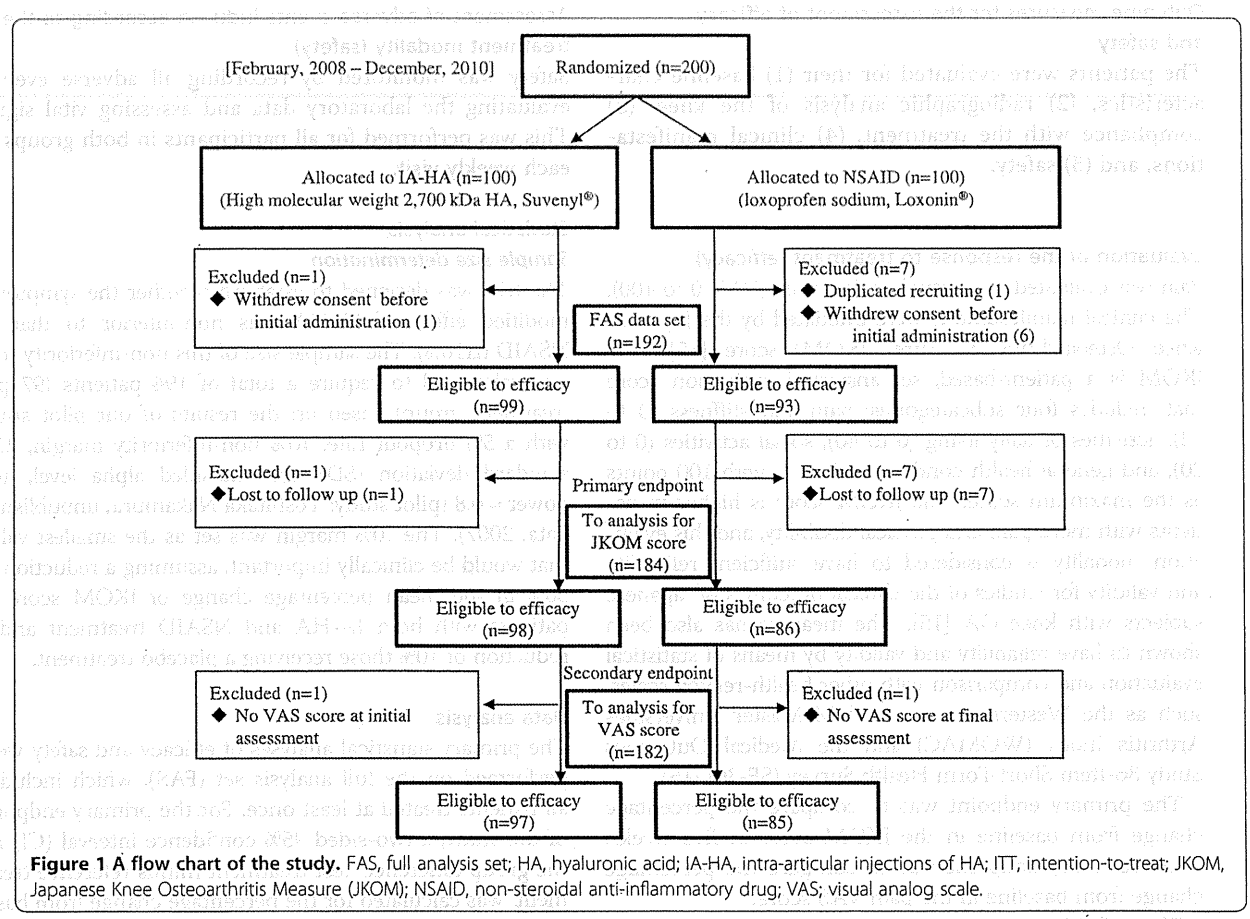

Figure 1 A flow chart of the study. FAS, full analysis set; HA, hyaluronic acid; IA-HA, intra-articular injections of HA; ITT, intention-to-treat; JKOM, Japanese Knee Osteoarthritis Measure (JKOM); NSAID, non-steroidal anti-inflammatory drug; VAS; visual analog scale.

randomly allocated into the NSAID group, and the other half allocated into the IA-HA group. Two patients in the IA-HA group and 14 patients in the NSAID group were excluded; therefore, the remaining 184 patients were included in the analyses of the primary endpoint.

The baseline patient characteristics are shown in Table 1. No significant statistical differences between the baseline characteristics of both groups were found.

Efficacy analyses (primary and secondary endpoints)

For the primary endpoint analysis, the JKOM score of the patients in both the NSAID group and in the IA-HA group was significantly reduced by the treatment ($P<0.001$, Table 2), and the percentage change from baseline in the JKOM score for the two groups was −32.2% and −34.7%, respectively. The difference in the percentage changes of the JKOM score between the two intervention arms (primary endpoint) was −2.5% (95% CI: -14.0 to 9.1%).

In a multiple regression analysis performed taking into consideration the factors considered to stratify the study design, the difference in the primary endpoint between the two intervention arms was also less than 10% (data not shown). These results demonstrate that the IA-HA treatment was non-inferior to the NSAID treatment for the percentage reduction in the clinical symptoms evaluated by the JKOM.

For the secondary endpoint analysis, the pain VAS score of the patients in the NSAID group was significantly

Table 1 Baseline characteristics of the patients in the study

		IA-HA (n = 99)	NSAID (n = 93)
Age (y)	Mean (SD)	68.2 (7.1)	68.5 (7.0)
Gender	Male	27	22
	Female	72	71
BMI	Mean (SD)	23.8 (3.4)	24.4 (3.6)
K/L grade	1	16	15
	2	48	50
	3	35	28
JKOM score (Min:0 - Max:100)	Mean (SD)	33.8 (15.8)	31.6 (14.1)
Pain VAS (Min:0 - Max:100)	Mean (SD)	60.3 (22.4)	55.1 (21.9)

IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug; BMI, body mass index; K/L, Kellgren-Laurence grade; JKOM, Japanese Knee Osteoarthritis Measure; VAS, visual analog scale.

Table 2 Results of the primary endpoint of the study

		JKOM score			% change of JKOM score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
IA-HA (n = 98)	Pre-treatment	33.8	15.9	<0.001	−34.7	39.6	−2.5 (−14.0 to 9.1)
	Post-treatment	21.5	14.6				
NSAID (n = 86)	Pre-treatment	32.0	14.0	<0.001	−32.2	39.8	
	Post-treatment	22.0	15.5				

The effect of the treatment of either IA-HA or NSAID for the patients with knee OA evaluated by JKOM score (left) and percentage (%) change of JKOM score (right). A *P* value less than 0.05 was considered to be significant. JKOM, Japanese Knee Osteoarthritis Measure; IA, intra-articular; HA. hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

reduced by the treatment ($P<0.001$, Table 3). The percentage change from baseline in the VAS score in the NSAID group was −36.0%. The pain VAS in the IA-HA group was also significantly reduced by the treatment, with a percentage change from baseline in the VAS score of −41.2% ($P<0.001$). The difference in the percentage changes in the pain VAS score between the two intervention arms (secondary endpoint) was −5.2% (95% CI: -23.8 to 13.4%).

Subanalyses

When the patients were divided into two groups (responders or non-responders) by the OMERACT-OARSI response criteria [16], 69.7% (69/99) of the patients in IA-HA group were classified as 'responders', while 62.4% responders were found (58/93) in the NSAID group. Again, there were no significant differences in the frequency of 'responders' between these two groups ($P = 0.283$).

A multiple logistic regression analysis, which was adjusted for age, K/L grade, BMI and the participating medical centers, confirmed the lack of significant differences in the odds ratio of responders between those who received IA-HA treatment and those who received NSAID treatment (odds ratios: 1.47 (95% CI: 0.761 to 2.83)).

We further investigated whether IA-HA is broadly effective from very early (K/L grade of 1) to moderate stages of knee OA (K/L grade of 3) (Table 4). Both IA-HA and NSAID groups significantly reduced the patient-oriented outcome measure evaluated by the JKOM score in the patients with both a K/L grade of 2 and 3. In patients with a K/L grade of 1, IA-HA treatment also reduced the JKOM score, but this reduction was not significant ($P = 0.058$). On the other hand, NSAID treatment of this group significantly reduced the JKOM score ($P = 0.001$).

Safety analyses

During the five weeks of examination, nine of ninety-nine patients (9.1%) in the IA-HA group were withdrawn from the study (one patient's symptoms improved and eight patients were lost to follow-up). Nineteen of ninety-three patients (20.4%) of NSAID group were withdrawn from the study (five patients experienced side effects, four withdrew consent, two patient's symptoms improved, and eight were lost to follow-up). The frequency of the withdrawal rate in the IA-HA group was significantly lower than that in the NSAID group ($P = 0.026$, Table 5).

Serious adverse events, including gastrointestinal (GI) hospitalization, were not observed in both groups during this study. As one patient complained of stiffness in the affected knee after injection, the frequency of adverse events in patients treated with the IA-HA was 1.0%. Ten (symptom related to GI tract disorder, seven; drug allergy, three) of ninety-three patients (10.8%) exhibited adverse events in those treated with the NSAID. The frequency of adverse events in the IA-HA group was significantly lower than that of those in NSAID group ($P = 0.004$, Table 5).

Discussion

This short-term trial clearly demonstrated that both the IA-HA at weekly intervals and daily oral NSAID over five weeks significantly improved both the clinical symptoms evaluated by the patient-oriented outcome measure

Table 3 Results of the secondary endpoint of the study

		Pain VAS			% change of VAS score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
IA-HA (n = 97)	Pre-treatment	60.1	22.4	<0.001	−41.2	52.7	−5.2 (−23.8 to 13.4)
	Post-treatment	31.8	24.1				
NSAID (n = 85)	Pre-treatment	55.5	21.8	<0.001	−36.0	73.8	
	Post-treatment	31.9	23.9				

The effect of the treatment of either IA-HA or NSAID for the patients with knee OA evaluated by pain VAS score (left) and percentage (%) change of VAS score (right). A *P* value less than 0.05 was considered to be significant. VAS, visual analog scale; IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

Table 4 JKOM score and percentage change of JKOM score by K/L grade subgroup

		JKOM score			% change of JKOM score		
		Mean	SD	*P* (post vs. pre)	Mean (%)	SD	Difference (%) [IA-HA - NSAID] (95% CI)
K/L grade 1							
IA-HA (n = 15)	Pre-treatment	24.8	13.0	0.058	−9.3	78.0	25.7 (−19.3 to 70.7)
	Post-treatment	18.7	12.6				
NSAID (n = 14)	Pre-treatment	35.9	15.4	0.001	−34.9	26.0	
	Post-treatment	23.4	15.7				
K/L grade 2							
IA-HA (n = 48)	Pre-treatment	33.1	14.7	<0.001	−43.8	27.1	−9.2 (−24.4 to 6.0)
	Post-treatment	18.8	12.6				
NSAID (n = 45)	Pre-treatment	30.8	13.9	<0.001	−34.6	44.9	
	Post-treatment	20.4	14.5				
K/L grade 3							
IA-HA (n = 35)	Pre-treatment	38.6	17.1	<0.001	−33.1	23.6	−6.2 (−21.6 to 9.3)
	Post-treatment	26.4	16.9				
NSAID (n = 27)	Pre-treatment	31.9	13.6	0.003	−26.9	37.0	
	Post-treatment	23.7	17.3				

A *P* value less than 0.05 was considered to be significant. JKOM, Japanese Knee Osteoarthritis Measure; IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug; K/L, Kellgren-Laurence grade.

and the pain severity evaluated by a VAS. No significant differences in the symptom-modifying effects were observed during this short period. In addition, the safety of the early phase of IA-HA treatment was superior to that of the NSAID in the patients with knee OA.

HA is a large glycosaminoglycan composed of repeating disaccharides of glucuronic acid and N-acetyl glucosamine that is naturally present in synovial fluid. Several protective properties of HA have been reported including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication [19]. Numerous clinical trials, meta-analyses and systematic reviews have indicated its clinical efficacy for knee OA [5,9,10,20]. Based on these previous findings, the OARSI recommendations that were revised in 2010 summarized the effect size (ES) of IA-HA at 0.60 (95% CI; 0.37, 0.83). However, as the ES declined to 0.22 (95% CI; -0.11, 0.54) when only the high-quality trials were selected [5], controversy remains regarding the efficacy of HA in treating knee OA [8]. A recent meta-analysis concluded that the pain reduction by IA-HA is observed later than that of intra-articular corticosteroids [9]. In addition, the effects of IA-HA for knee OA pain continued over six months post-intervention [10]. However, few studies have been conducted to clarify the early effects and safety of IA-HA in comparison to those of NSAIDs. The results of this study clearly indicated that the early efficacy of IA-HA was not inferior in comparison to that of the NSAID.

Table 5 Withdrawal and harmful events during the study

Withdrawn	Completed	Withdrawn	Frequency (%)	*P*
IA-HA (n = 99)	90	9	9.1	0.026
NSAID (n = 93)	74	19	20.4	
Harmful events	**Not occurred**	**Occurred**	**Frequency (%)**	***P***
IA-HA (n = 99)	98	1	1.0	0.004
NSAID (n = 93)	83	10	10.8	

IA, intra-articular; HA, hyaluronic acid; NSAID, non-steroidal anti-inflammatory drug.

A number of HA products with a variety of the molecular weights, ranging from approximately 600 to 6,000 kDa, have been developed as IA-HA for the treatment of OA [8]. The considerable heterogeneity of outcomes between trials may be due in part to differences in HA products [5]. High-molecular-weight HA (>6,000 kDa) is suggested to have greater effects in comparison to lower-molecular-weight HA [8]. On the other hand, the intra-articular injection of high-molecular-weight HA (>6,000 kDa) showed a greater frequency of adverse events, such as pain flares, and hot and swollen knees, which typically occurred 24 to 72 hours after injection [21]. There were no cases of painful, hot or swollen knees during the study.

The molecular mechanisms underlying the efficacy of IA-HA for OA remain unclear. OA is frequently associated with the signs and symptoms of inflammation, including joint pain, swelling and stiffness leading to significant functional impairment and disability [2]. Synovitis plays an important role in inducing the pain, swelling and stiffness in OA [22], and the severity of synovitis is well correlated with the JKOM score of the patients with knee OA [23]. It has recently been reported that HA inhibits the activities of matrix

metalloproteinases and aggrecanases which are, at least in part, involved in OA cartilage degradation as a result of their induction by proinflammatory cytokines, such as interleukin (IL)-1 [19,24-26]. Therefore, HA is speculated to modify the structural damage of joints and the rate of OA progression in addition to the symptom-modifying effect [27], although further studies are required.

In this trial, the early efficacy of IA-HA was compared with that of NSAID for the treatment of knee OA. NSAIDs have also been proven to be an effective conservative treatment for knee OA [5]. However, a high incidence of serious GI tract adverse events associated with the use of oral NSAIDs was also demonstrated in a population-based cohort study of older patients [28]. In addition, the hospitalization due to GI tract side effects in patients receiving non-selective NSAIDs was twice as high as that in those given the cyclooxygenase (Cox)-2 selective agent, celecoxib, or a non-selective NSAID together with a PPI [28]. Although a PPI was not routinely used in addition to the NSAID (loxoprofen sodium) in this study, no serious GI events were noted.

Since chronic kidney disease (CKD), which is similar to knee OA, is also a prevalent disease especially in older populations, knee OA patients with CKD may have a different risk profile and treatment response than knee OA patients without CKD. However, as patients with renal disorders were excluded in the present study, as described in the Methods section, whether the presence of CKD has any effect on the efficacy and safety of either the IA-HA or NASIDs remains unclear.

The efficacy of IA-HA for knee OA has been debated for over a decade. Although it has been systemically evaluated in meta-analyses, most previous studies have focused on comparing the findings with either placebo or intra-articular corticosteroids [9,10,29]. No previous studies have undertaken a meta-analysis with NSAIDs, which is one of the most efficacious and widely used treatments for knee OA [5]. The present study clearly shows that IA-HA is as effective as continuous NSAID use at five weeks of treatment, and, in addition, it showed a more favorable safety profile of IA-HA over NSAIDs for knee OA. The present study suggests that future randomized trials should thus be carried out with a longer duration of follow-up and larger samples, in order to identify optimal knee OA treatment alternatives. Furthermore, it would also be interesting to evaluate whether any synergistic effect of these two combined treatments exists when they are combined.

The current study does have some limitations. First, this investigation was an open-label randomized trial and not a double-blind controlled trial. Therefore, the design may have introduced certain bias into the results. Second, the trial's size was calculated to have sufficient power to exclude a 10% between-group percentage change of JKOM score, which can be debated. This margin was supported by our pilot study, as described previously. Third, in subgroup analysis for the patients with a K/L grade of 1, IA-HA treatment reduced the JKOM score. However, this reduction was not statistically significant ($P = 0.058$). Although the reason for this is unclear, the interpretation of the result was limited by the small number of patients (n = 15) and, therefore, it may be one of the limitations. Even though some subjects had a K/L grade of 1, some have an increased risk for rapid progression of the disease [30]. Unfortunately, we cannot predict radiographically who is at risk for progression [4].

Conclusions

The early efficacy of IA-HA is suggested to be not inferior to that of a NSAID, and the safety of the early phase of IA-HA is superior to that of a NSAID for patients with knee OA.

Abbreviations

ACR: American College of Rheumatology; BMI: body mass index; CKD: chronic kidney disease; FAS: full analysis set; GI: gastrointestinal; HA: hyaluronic acid; IA-HA: intra-articular injections of HA; JKOM: Japanese Knee Osteoarthritis Measure; K/L: Kellgren-Lawrence; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology Clinical Trials; PPI: proton pump inhibitor; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

As principal investigators of this study, all authors of this study had full access to all data, and take responsibility for their integrity and the accuracy of their analysis. TN, KS, KH, HKu and KK participated in the study design. HKu and KK supervised the study. MI, TN, KS, HKi, SS, GO, TY, YU, JC, MK and HKu collected the data. MI, YI and KH analyzed the data. YI and KH provided statistical expertise. MI and KH drafted the manuscript, and the manuscript was revised for content by MI, TN, KS, KH, HKi, SS, GO, TY, YU, JC, YI, MK, HKu and KK. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Osteoporosis, vertebral fractures and mortality in a Japanese rural community

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Abstract

Objectives. The present study aims to determine the relationship between osteoporosis (OP), vertebral fracture (VF) and mortality.

Methods. We followed up 1024 residents of Miyagawa village every 2 years for a mean of 8.4 years between 1997 and 2009. The residents were assessed every 2 years. We defined OP as T scores for bone mineral density that were < 2.5 standard deviations below peak bone mass. VF was assessed by lateral radiography of the thoracic and lumbar spine. The participants were allocated as follows depending on the presence or absence of OP and VF: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group). We determined survival/mortality rates until 2011 by reviewing medical histories and death certificates.

Results. By 2011, 304 participants had died. The respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. Mortality rates were significantly worse for the OP + VF group than the Control group (OP + VF Hazard Ratio: 1.89; 95% CI, 1.27–2.77).

Conclusion. Prevention of osteoporotic VF in elderly persons is very important from the viewpoint of increasing life expectancy.

Keywords

Elderly, Epidemiology, Mortality, Osteoporosis, Vertebral fractures

History

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Introduction

Osteoporosis (OP) is characterized by increased bone loss and enhanced bone fragility. Japanese society is rapidly aging. Yoshimura et al. [1] described that about 6.4 and 11 million individuals in Japan have L2–4 and femoral neck OP. Therefore, OP and osteoporotic fractures are major public health problems in this aging society.

Vertebral fractures (VF) are the most common type of osteoporotic fracture, with an estimated annual incidence of 700 000 in the US [2] and 1.4 million in Europe [3]. Elderly persons typically develop VF due to bone fragility caused by OP. However, VF are sometimes caused by high-velocity accidents, such as car crashes or falls from a considerable height. Morphological evaluation by radiography alone cannot easily differentiate whether or not VF result from high-velocity accidents involving osteoporotic bone. However, the possibility that a combination of OP and VF causes osteoporotic VF might be quite high.

Some investigators have reported that low bone mineral density (BMD) is a risk factor for death [4,5]. If OP is independently associated with mortality, increased mortality might be associated with other types of osteoporotic fractures. Many studies have shown that osteoporotic [6–9], particularly hip [10–13], fractures are associated with increased mortality. Several recent studies of VF have also found that mortality is higher in patients with OP than in the general population [6,14–16]. However, Cummings and Melton [17] noted that most VF are subclinical or remain unrecognized without radiographic examination. Haczynski and Jakimiuk [16] also noted only one third of all VF are diagnosed clinically. Many studies have evaluated clinical (symptomatic) VF, but few have described mortality rates based on prevalent, radiographically defined VF [18,19].

We tested the hypothesis that osteoporotic, radiographic VF is associated with an increased risk of death among Japanese community dwellers.

Materials and methods

This population-based study of the residents of Miyagawa, a rural mountain village located in the center of Mie Prefecture, Japan, began in 1997. The participants were self-recruited, community-dwelling volunteers aged ≥ 65 years, who were assessed every 2 years from 1997 to 2011 at Houtoku Hospital for a total of eight studies. The population of the village in 1997 and 2010 was 4196 and 3490, respectively, when 1463 and 1553 residents, respectively, met the age criterion. This study proceeded at a local hospital, so participants had to arrive by public transportation or by other means, and they also had to understand the purpose of the study. Thus, the participants were generally healthier than non-participants.

Of 1271 residents (806 women and 465 men) who participated in these studies at least once, 1024 (661 women and 363 men) who

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were followed up for a mean of 8.4 (1–14) years were included in the study.

The Committee for the Ethics of Human Research at Mie University approved the study protocol, and all participants provided written, informed consent before enrollment.

Baseline data obtained from standard questionnaires administered by orthopedic surgeons included information regarding age, gender and medical history. Body–mass index (BMI) was calculated from height and weight. Other medical examinations comprised radiography of the thoracic and lumbar spine and assessments of BMD at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). We defined OP as T scores of BMD < 2.5 standard deviations (SD) below peak bone mass according to the World Health Organization criteria [20]. Central DXA of the lumbar spine or femoral neck is generally used to diagnose OP. However, many elderly individuals have vertebral deformities. Thus, lumbar DXA tends to show high BMD. Positioning (degree of internal rotation) of the femoral neck for DXA is difficult and thus reproducibility is poor and femoral DXA is unsuitable for longitudinal studies. Therefore, we assessed the participants using radial DXA.

We assessed VF from lateral radiographs of the thoracic and lumbar spine in terms of a wedge, biconcave or crushed appearance according the Japanese Society of Bone and Mineral Research criteria [21].

Based on the baseline OP and VF criteria, the participants were allocated to the following groups: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group).

We assessed the survival/mortality rates of the participants until 2011 by reviewing their medical histories and death certificates with the help of local hospital staff. Causes of death were determined from death certificates.

Statistical analysis

Means ± SD were calculated for variables unless otherwise noted. Significant differences in baseline characteristics between the OP and Control groups, between the VF and Control groups, and between the OP + VF and Control groups were determined using t and χ^2 tests. Survival curves for the OP, VF, OP + VF and Control groups were constructed based on the Kaplan–Meier method. We also used Cox proportional hazards analyses to determine age–gender-adjusted mortality (as hazard ratios [HR] and 95% confidence intervals [CI]) among three groups (OP, VF and OP + VF groups) and the Control group. The Control group served as the reference for the Cox proportional hazards analyses. The period of the Cox model was measured in months. The significance level for entry into the model was 0.05. All data were statistically analyzed using PASW Statistics version 18 software (SPSS, Chicago, IL, USA).

Table 1. Baseline physical characteristics of all groups.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$
Gender (M/F)	9/116*	33/323*	40/19	281/201
Age (y)	77.1 ± 7.6*	72.2 ± 6.6*	72.1 ± 6.1	70.8 ± 5.6
Height (cm)	143.1 ± 7.6*	147.7 ± 7.0*	154.5 ± 7.4	154.8 ± 7.5
Weight (kg)	46.9 ± 10.0*	49.9 ± 8.4*	55.6 ± 10.1	56.6 ± 8.4
BMI (kg/m^2)	22.8 ± 3.9†	22.8 ± 3.3*	23.2 ± 3.6	23.6 ± 3.0

BMI, body–mass index; F, female; M, male; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.01$ and †$p < 0.05$ versus Control.

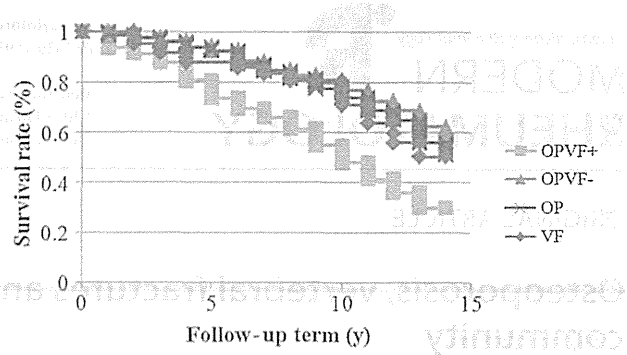

Figure 1. Survival rates for all groups. OP, osteoporosis; VF, vertebral fractures.

Results

The overall mean age of participants was 72.1 ± 6.5 years (average for men and women, 72.4 ± 6.3 and 72.0 ± 6.7, respectively). During a mean follow-up of 8.4 years, 304 participants (29.7%) had died. Table 1 compares the physical characteristics among the four groups. Height, weight and BMI were significantly lower, whereas the ratio of females and age were significantly higher for the OP + VF and OP groups than for the Control group.

Figure 1 shows the Kaplan–Meier survival curves for the four groups. The respective 5- and 10-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2% and 54.9%, 77.4%, 80.7% and 79.8%. Table 2 shows the results of the age and gender-adjusted Cox proportional hazards analyses. The mortality was significantly worse for the OP + VF group than for the Control group. The HR for the OP + VF group was 1.89 (95% CI, 1.27–2.77). The mortality rate tended to be worse for the OP group, but the difference did not reach significance.

Table 3 shows the causes of the 304 deaths. Malignant tumors, heart disease, old age, accidents, suicide, other and unknown causes accounted for 24.7%, 18.8%, 3.3%, 3.6%, 2.0%, 12.5% and 8.9%, respectively, of the deaths. These data were similar to the national data for Japan during 2009 [22]. The causes of death did not significantly differ among the four groups.

Discussion

We recognized the combination OP and VF (OP + VF group) as osteoporotic VF, and found that this combination was associated with high mortality rates among a Japanese village community.

Johnell et al. [15] and Cooper et al. [6] reported 5-year survival rates for individuals with VF of 28% in Sweden, and 61% in the USA, respectively. Our rates of all groups were higher than these findings, which might have been due to our study cohort being generally healthier.

Some authors [4,5] have reported that low BMD is a risk factor for death, and that it is probably related to comorbidity in affected patients. Of course, OP predisposes bones to easy breakage and

Table 2. Age and gender-adjusted Cox proportional hazards findings versus Control.

	Alive	Dead	HR	95% CI	DF	P
					3	0.01
Control	360	124	1			
OPVF+	64	61	1.88	1.27–2.77	1	< 0.005*
OP	255	101	1.33	0.98–1.81	1	0.07
VF	41	18	0.91	0.55–1.49	1	0.70

95% CI, 95% confidence intervals; HR, hazard ratio; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.005$ versus Control.

Table 3. Causes of death.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$	Total $n = 1024$
Malignant tumor	11	21	3	40	75
Heart disease	10	18	3	26	57
Pneumonia	6	17	5	22	50
Brain disease	4	14	2	10	30
Old age	4	5	0	1	10
Accident	2	5	2	2	11
Suicide	2	2	1	1	6
Other	17	9	1	11	38
Unknown	5	10	1	11	27
Total	61	101	18	124	304

OP, osteoporosis; VF, vertebral fractures.

the relationship between OP and subsequent mortality might explain why survival decreases after sustaining osteoporotic fractures such as those of the hip [23]. In fact, a few studies have found that increased mortality is indeed associated with hip fractures [23–25]. Kanis et al. [26] reported that about 23% of deaths involving hip fractures might be causally related to the fracture itself. However, some [27–29] have shown that OP is associated with atherosclerosis, whereas others [30,31] have shown that OP does not increase the risk of mortality associated with fractures but is rather due to cardiovascular disease. The present study found that only OP without VF tended to associate with mortality, but a significant relationship was not identified ($p = 0.07$). Further study is needed to clarify this issue.

In term of causes of death, Kado et al. [14] reported that women with VF were 2- to 3-fold more likely to die of pulmonary causes than those without fractures. They also explained that severe kyphosis was highly predictive of pulmonary death, perhaps because those with underlying lung disease and decreased respiratory reserves might not be able to tolerate restrictive changes in thoracic anatomy resulting from VF. Indeed, Leech et al. [32] described a 9% decrease in predicted forced vital capacity per VF. Our preliminary report [19] associated the number of VF with mortality. Moreover, multiple VF might cause esophageal hiatal hernia and esophagitis [33,34], and restrict physical function, activities of daily living and quality of life [35,36]. Kado et al. [14] and Cooper et al. [6] also associated VF with increased cancer mortality. Thus, previous reports have associated VF with various causes of death. The present study associated the combination of VF and OP with increased mortality, but without relevance to a specific cause of death. Further investigation is needed to clarify the causes of death associated with osteoporotic VF.

Our study has several limitations. First, Miyagawa village is a rural mountain community, and many of the inhabitants are typically engaged in forestry. Thus, whether the present findings reflect the general population of Japan is doubtful. Second, participants who could attend the hospital were generally healthier than non-participants. Third, this investigation was based on a relatively small cohort. Therefore, the statistical significance of the risk factors might be relatively low. Fourth, since VF was evaluated only by radiographic morphometry and not clinically, we could not investigate differences between clinical and morphological VF.

In conclusion, the respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. The mortality rate was worse for elderly individuals with than without OP combined with VF (osteoporotic VF). Since osteoporotic VF increased the mortality rate 2-fold, efforts should be directed toward preventing such fractures in elderly populations to decrease mortality rates and increase life expectancy.

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Conflict of interest

None.

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Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment

*The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration**

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Summary

Background High blood pressure, blood glucose, serum cholesterol, and BMI are risk factors for cardiovascular diseases and some of these factors also increase the risk of chronic kidney disease and diabetes. We estimated mortality from cardiovascular diseases, chronic kidney disease, and diabetes that was attributable to these four cardiometabolic risk factors for all countries and regions from 1980 to 2010.

Methods We used data for exposure to risk factors by country, age group, and sex from pooled analyses of population-based health surveys. We obtained relative risks for the effects of risk factors on cause-specific mortality from meta-analyses of large prospective studies. We calculated the population attributable fractions for- each risk factor alone, and for the combination of all risk factors, accounting for multicausality and for mediation of the effects of BMI by the other three risks. We calculated attributable deaths by multiplying the cause-specific population attributable fractions by the number of disease-specific deaths. We obtained cause-specific mortality from the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. We propagated the uncertainties of all the inputs to the final estimates.

Findings In 2010, high blood pressure was the leading risk factor for deaths due to cardiovascular diseases, chronic kidney disease, and diabetes in every region, causing more than 40% of worldwide deaths from these diseases; high BMI and glucose were each responsible for about 15% of deaths, and high cholesterol for more than 10%. After accounting for multicausality, 63% (10·8 million deaths, 95% CI 10·1–11·5) of deaths from these diseases in 2010 were attributable to the combined effect of these four metabolic risk factors, compared with 67% (7·1 million deaths, 6·6–7·6) in 1980. The mortality burden of high BMI and glucose nearly doubled from 1980 to 2010. At the country level, age-standardised death rates from these diseases attributable to the combined effects of these four risk factors surpassed 925 deaths per 100 000 for men in Belarus, Kazakhstan, and Mongolia, but were less than 130 deaths per 100 000 for women and less than 200 for men in some high-income countries including Australia, Canada, France, Japan, the Netherlands, Singapore, South Korea, and Spain.

Interpretation The salient features of the cardiometabolic disease and risk factor epidemic at the beginning of the 21st century are high blood pressure and an increasing effect of obesity and diabetes. The mortality burden of cardiometabolic risk factors has shifted from high-income to low-income and middle-income countries. Lowering cardiometabolic risks through dietary, behavioural, and pharmacological interventions should be a part of the global response to non-communicable diseases.

Funding UK Medical Research Council, US National Institutes of Health.

Introduction

Cardiovascular diseases, chronic kidney disease, and diabetes are among leading global and regional causes of death.[1,2] Between 1990 and 2010, the total number of deaths caused by cardiovascular diseases increased by more than 25% and those of chronic kidney disease and diabetes nearly doubled.[1] Adiposity and high blood pressure, cholesterol, and glucose are important modifiable risk factors for cardiovascular diseases and (except for cholesterol) for chronic kidney disease.[3–6] Adiposity is also the most important modifiable risk factor for diabetes.[3,4,7] Over the past few decades, these risk factors have had divergent trajectories in many countries. While BMI and blood glucose have increased in most countries and worldwide,[8,9] mean blood pressure has fallen in high-income and some middle-income regions; it has remained unchanged or even increased in some low-income and middle-income countries.[10] Mean serum total cholesterol has also fallen in many parts of Europe, north America, and Australasia while increasing in east and southeast Asia, especially China, Japan, and Thailand.[11]

Previous comparative risk assessments[12,13] have reported global and some regional estimates of the effects of cardiometabolic risk factors on mortality. However, these studies did not analyse the combined effects of the risk factors, partly because reliable estimates of how much of the effect of adiposity on cardiovascular diseases is mediated through blood pressure, blood glucose, and serum cholesterol concentration were unavailable at the time.[14] The only analysis[15] of the combined effects of these risks divided the world into

three large regions and did not include high blood glucose as a risk factor. Additionally, previous studies used broad disease categories—for example, all cardiovascular diseases, rather than specific diseases of public health or clinical relevance such as stroke subtypes. Finally, very little is known about how much the effects of these risk factors on mortality have changed over time, even though both the prevalence of risk factors and cardiometabolic death rates have changed enormously, sometimes in opposite directions. We estimated cause-specific mortality from cardiovascular diseases, chronic kidney disease, and diabetes attributable to the effects of high BMI, blood pressure, blood glucose, and serum cholesterol, individually as well as in combination, by country and region from 1980 to 2010.

Methods

Data sources

We used measures of exposure to cardiometabolic risk factors for which the most comprehensive worldwide data were available—namely, BMI, fasting plasma glucose, systolic blood pressure, and serum total cholesterol. We derived population exposure to risk factors by country, year, sex, and age group from pooled analyses of population-representative health surveys as described in detail elsewhere.[8–11] Briefly, we collated population-based data from published and unpublished national, subnational, and community surveys and studies done between 1980 and 2010. We used 960 data sources across countries and years for BMI, 786 for systolic blood pressure, 370 for fasting plasma glucose, and 321 for total cholesterol.[8–11] About 50% of data for BMI in low-income and middle-income countries were from the 2000s and another 34% from the 1990s, whereas for high-income regions, data were evenly distributed over time.[9] The data for systolic blood pressure were distributed almost equally among the three decades of analysis, but more than 60% of national sources were from the 2000s.[10] About 40% of all data for total cholesterol and two-thirds of all national data were from the 2000s.[11] Half of the data for fasting plasma glucose and 68% of the national data, were from the 2000s, and another 35% from the 1990s.[8]

We used a Bayesian hierarchical model to estimate the levels of risk factors by sex and age group for all countries and years, sharing and borrowing information across space, time, and age as well as through covariates that helped predict risk factor levels.[8–11,16] The uncertainties of the estimates incorporated the sampling error of the data, as well as uncertainty resulting from some data sources not being nationally representative and from missing data. We estimated the standard deviations (SDs) of distributions of risk factors for each country-year-age-sex unit using the population mean and the coefficients of a regression that related SD to mean. We corrected SDs for systolic blood pressure, total cholesterol, and fasting plasma glucose for the error associated with one-off measurements by use of coefficients from prospective studies with multiple measurements.[17–19]

We quantified the effects of each risk factor on specific cardiovascular disease outcomes (ischaemic heart disease, ischaemic and haemorrhagic strokes, hypertensive heart disease, and other cardiovascular diseases), diabetes, and chronic kidney disease when there was evidence of a convincing or probable causal association.[3] For each risk factor–disease pair, we used the age-specific relative risk (RR) from meta-analyses of prospective studies that had adjusted for major confounders and to the extent possible for regression dilution bias. The RRs for effects on cardiovascular diseases and diabetes are reported elsewhere, as is the RR for the effect of high BMI on chronic kidney disease.[3,4,20] The RR for the effect of high blood pressure on chronic kidney disease from pooled analysis of prospective cohorts was 1·28 (1·18–1·39) per 10 mm Hg higher systolic blood pressure (unpublished data).

We estimated what proportion of the effects of BMI on ischaemic heart disease and stroke was mediated through the other three risk factors from a pooled analysis of 97 prospective cohort studies.[14] This pooled analysis showed that 46% (95% CI 42–50) of the excess RR of BMI on ischaemic heart disease and 76% (65–91) on stroke were mediated through the other three risk factors.[14] We assumed that the effect of high BMI on hypertensive heart disease is fully mediated through blood pressure, on diabetes through fasting plasma glucose concentration, and on chronic kidney disease through the combination of systolic blood pressure and fasting plasma glucose concentration.

We used estimates of the number of deaths by underlying cause from the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study, with data sources and methods described in detail elsewhere.[1] Briefly, total and cause-specific death rates were estimated from data from vital registration, sample death registration systems, verbal autopsy studies, censuses, household surveys, and mortuaries. Deaths assigned to impossible and improbable causes of death were re-distributed, and statistical models were used to estimate cause-specific death rates by country, year, sex, and age group, with specific models selected on the basis of data quality and performance of the model. Like risk factors, there were substantially more data for causes of death in recent years than for the 1980s.[1]

Statistical analysis

We calculated population attributable fractions, which quantify the proportion of deaths from each cause that would have been prevented if the risk factor distribution had been set to an optimal level in the population. We calculated population attributable fractions as described elsewhere,[12,13,21] using data for exposure distributions and RRs for each risk factor–disease pair. The number of

deaths attributable to each risk factor is a product of the population attributable fraction and the cause-specific deaths for each country-year-sex-age group unit. The optimal levels were based on the levels corresponding to lowest all-cause mortality from reliable epidemiological studies.[3] To account for the uncertainty of these optimal distributions, we allowed them to take a range with means of 110–115 mm Hg (SDs 4–6) for systolic blood pressure; 3·8–4·0 mmol/L (0·50–0·65) for total cholesterol; 21–23 kg/m² (1·1–1·8) for BMI; and 4·9–5·3 mmol/L (0·4–0·6) for fasting plasma glucose.[3] The benefits of lowering BMI for haemorrhagic stroke were estimated only for values above 25 kg/m², because there seems to be no reduction in risk below this level.[4]

The number of cause-specific deaths attributable to multiple risk factors is often less than the sum of those attributable to individual risk factors because some deaths are the result of more than one risk factor (multicausality), and because some of the effects of BMI are mediated through the other three risk factors.[14] In the absence of mediation, effect modification, and risk factor correlation, the combined effects of multiple risk factors can be calculated on the basis of their individual population attributable fractions using a simple relationship that incorporates multicausality as described elsewhere.[15] To use this relationship in the presence of mediation, we calculated the direct effect of BMI on the relevant disease outcomes (ie, the part not mediated by the other three risks). We then tested the sensitivity of our findings to the correlation between risk factors. We used both an empirical correlation matrix from the continuous US National Health and Nutrition Examination Survey 1999–2010 (with pairwise correlation coefficients of between 0·11 and 0·31) and another correlation matrix with substantially larger pairwise correlation coefficients of 0·8.

For the **US National Health and Nutrition Examination Survey 1999–2010** see http://www.cdc.gov/nchs/nhanes.htm

Our analysis covered 187 countries for which estimates of deaths by cause were available. We obtained regional and worldwide results by population weighting country estimates. We combined age-specific death rates into broader ages (25–69 and ≥70 years). We calculated age-standardised death rates with use of the WHO standard population.[22]

We propagated the uncertainties of all inputs (risk factor exposure distributions, RRs, proportion of excess risk from BMI mediated through the other three risks, and cause-specific deaths) to the final estimates with a simulation approach. Specifically, we used 1000 draws from the uncertainty distributions of each input, and repeated the calculations with these draws. The resulting 1000 population attributable fractions and attributable deaths characterised the distributions of the outputs. We report the median of these draws as the central estimates and their 2·5th and 97·5th percentiles as the 95% credible or confidence interval. Draws for different analysis units might be correlated (eg, in two age groups or countries for risk factor exposures and cause-specific deaths because they came from a common statistical model). We took these correlations into account by taking correlated draws across countries, age groups, and years. We did all statistical analyses with Stata (version 12.0) and R (version 3.02).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. YL, GMS, and EC together had full access to all data used in this study. ME was responsible for submitting the article for publication.

Results

Between 1980 and 2008, age-standardised global mean BMI increased by 0·4 kg/m² per decade (95% CI 0·2 to 0·6) for men and 0·5 kg/m² per decade (0·3 to 0·7) for women. Mean BMI for men increased in every region except central Africa and south Asia, with the largest increase in Oceania. The largest rise in women's BMI also occurred in Oceania, followed by southern and central Latin America. BMI did not change for women in central and eastern Europe and central Asia. Between 1980 and 2008, worldwide systolic blood pressure fell by 0·8 mm Hg per decade (95% CI −0·4 to 2·2) for men and 1·0 mm Hg per decade (−0·3 to 2·3) for women. Systolic blood pressure decreased most in high-income countries for men and women. Systolic blood pressure rose in Oceania, east Africa, south Asia, and southeast Asia for both sexes, and in west Africa for women. Globally, mean serum total cholesterol concentration changed little between 1980 and 2008, falling by less than 0·1 mmol/L per decade for men and women. Total serum cholesterol fell in Europe, Australasia, and north America but increased in east and southeast Asia and Pacific. We found little evidence of a change in Latin America and the Caribbean, the Middle East and north Africa, south Asia, and sub-Saharan Africa. Global age-standardised mean fasting plasma glucose increased by 0·07 mmol/L per decade (95% CI −0·02 to 0·15) for men and 0·09 mmol/L per decade (0·00 to 0·17) for women, with increases or, at best, no change in every region. The largest increase in fasting plasma glucose occurred in Oceania. Risk factor trends by country and region are described in detail elsewhere.[8–11]

In 2010, cardiovascular diseases, chronic kidney disease, and diabetes were together responsible for 17·6 million (33%) of 52·8 million deaths worldwide.[1] The number of deaths from these causes attributable to individual cardiometabolic risks ranged between 2·0 (1·5–2·5) million for high serum cholesterol and 7·7 (6·9–8·4) million for high blood pressure. After accounting for multicausality, the four risk factors together were responsible for 63% (10·8 million, 95% CI 10·1–11·5) of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes, accounting for one in every five deaths worldwide. These deaths were divided

almost equally between men (5·5 million, 5·0–5·9) and women (5·3 million, 4·7–5·8; figure 1A). The combined mortality burden of the four risk factors was 7·1 million (67%) of 10·6 million deaths worldwide (95% CI 6·6–7·6) in 1980, increasing steadily throughout the three decades of analysis, driven by population growth and aging. Although high blood pressure was the leading risk factor throughout the analysis period, high cholesterol was responsible for the second most deaths until 1990. High BMI and blood glucose had smaller effects in 1980, each responsible for around 1·2 million deaths; this number had doubled by 2010.

After accounting for population size and aging, age-standardised deaths attributable to the four risk factors fell steadily worldwide, and in high-income regions, Latin America and the Caribbean, and the Middle East and north Africa, between 1980 and 2010 (figure 2). In high-income regions, this fall was caused by a combination of decreasing population attributable fractions (themselves driven by lower systolic blood pressure and total serum cholesterol) and lower cardiovascular death rates; elsewhere, falling mortality was the main driver.[23,24] Age-standardised death rates attributable to risk factors increased in south Asia because both risk factor levels and total death rates increased; they did not change in sub-Saharan Africa and decreased only slightly in central and eastern Europe and central Asia. There was, however, a steeper decline in central and eastern Europe and central Asia after 2000.

In 1980, the number of deaths attributable to these four risk factors in high-income regions was larger than that in any of the low-income and middle-income regions; high-income regions accounted for 35% (2·5 milion of 7·1 million) of deaths attributable to the combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol, whereas low-income and middle-income regions accounted for the remaining 65% (figure 1A). By 2010, low-income and middle-income regions accounted for 82% (8·8 million of 10·8 million) of attributable deaths, and the two regions with the largest number of attributable deaths were east and southeast Asia and Pacific (3 million deaths or 28% of all deaths attributable to these risks), followed by central and eastern Europe and central Asia (2 million deaths). In fact, from 1980 to 2010, the number of deaths attributable to high blood pressure and cholesterol fell in high-income regions, despite population increase and aging, and those attributable to high BMI and blood glucose increased only slightly. In low-income and middle-income regions, the number of deaths attributable to these four risk factors increased or remained stable over time. In 2010, east and southeast Asia and Pacific also had the largest mortality burden of high blood glucose and blood pressure—30% of deaths attributable to high blood pressure worldwide occurred in this region. However, mortality burden of high BMI and serum cholesterol were still largest in high-income regions and in central and eastern Europe and central Asia in 2010.

40% (4·3 million of 10·8 million) of deaths attributable to these four risk factors in 2010 occurred in people aged younger than 70 years and thus caused greater loss of life years than deaths of older people (figure 1B). Deaths before age 70 years made up a smaller proportion of the mortality burden of the four risk factors in high-income regions (21% of all attributable deaths) and in central and eastern Europe and central Asia (33%) than in other regions. The share of attributable deaths before age 70 years was greatest in south Asia (55%) and sub-Saharan Africa (58%). Deaths attributable to the four risk factors shifted to older ages over time in high-income regions, where 31% of deaths attributable to the risk factors occurred in people younger than age 70 years in 1980 (compared with 21% in 2010). A similar shift occurred in Latin America and the Caribbean but not in other regions.

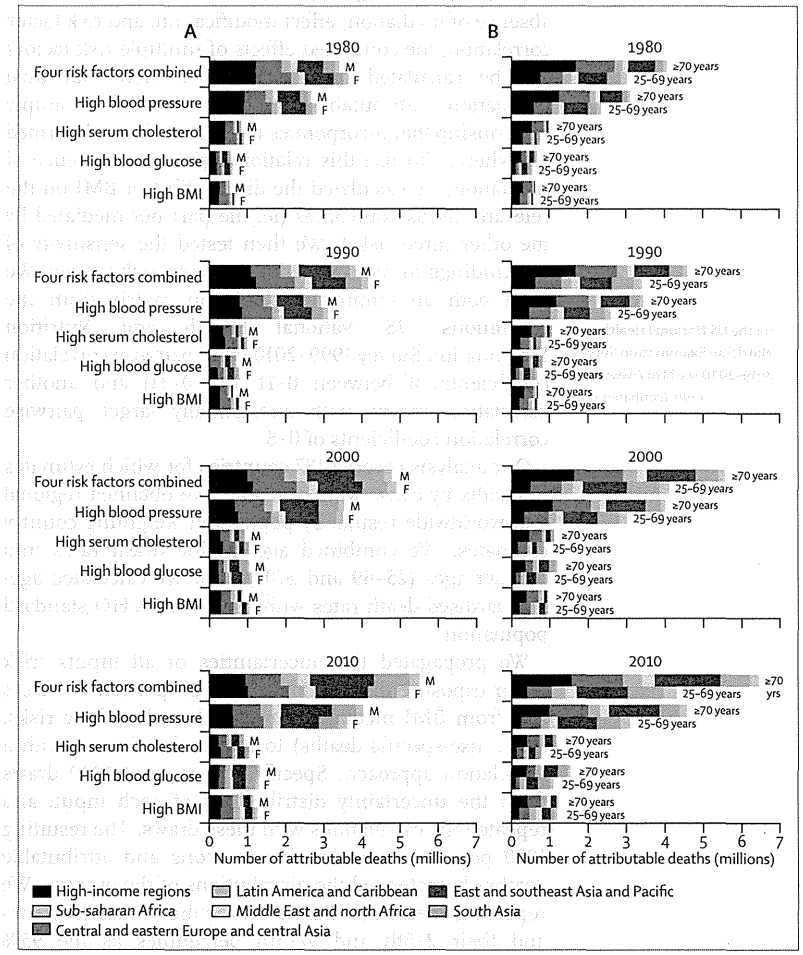

Figure 1: **Deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to the individual and combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose by region and sex (A) and age group (B), 1980–2010**
M=male. F=female.

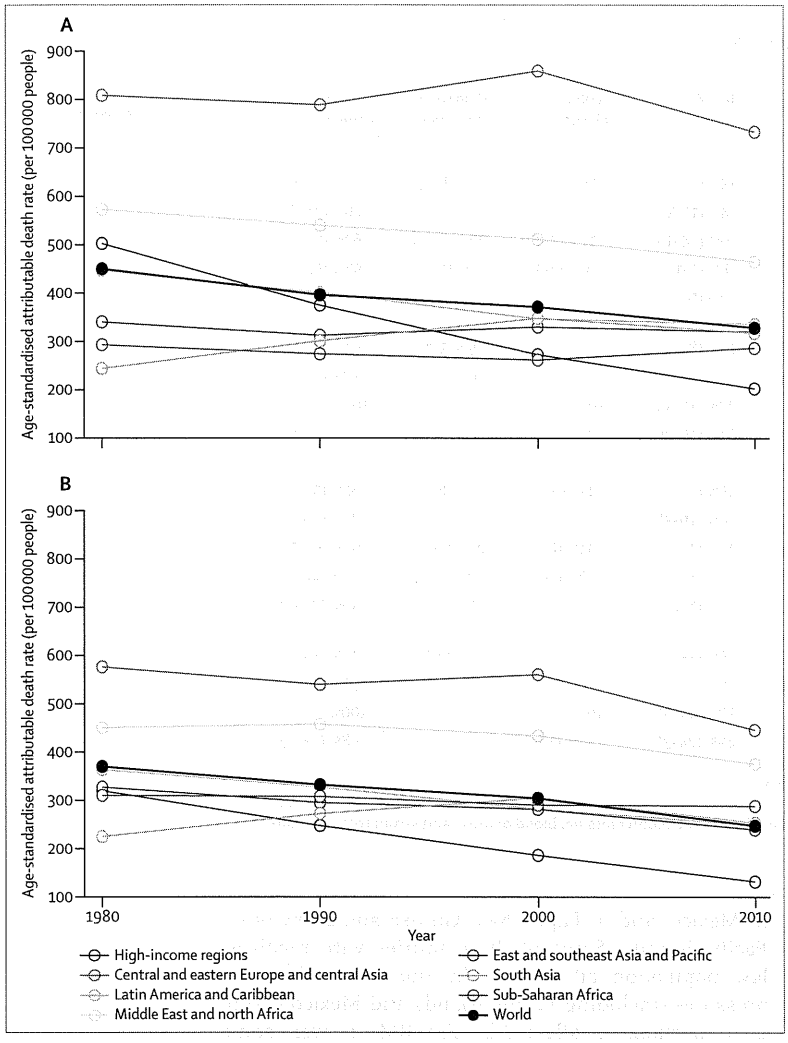

Figure 2: **Age-standardised death rates from cardiovascular diseases, diabetes, and chronic kidney disease attributable to the combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose by region for men (A) and women (B)**

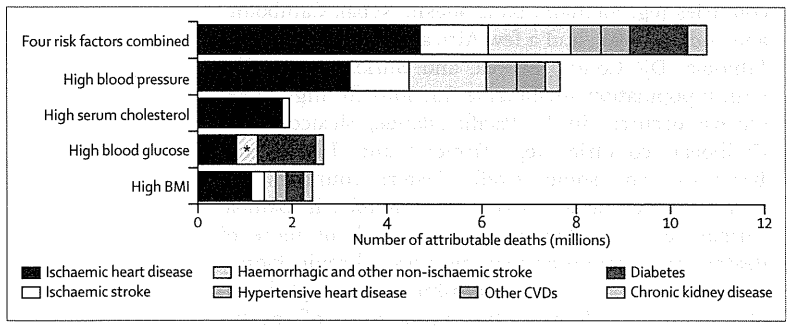

Figure 3: **Deaths attributable to the individual and combined effects of high BMI, blood pressure, serum cholesterol, and blood glucose in 2010, by disease**
CVD=cardiovascular disease. *For total stroke (RRs were for association between blood glucose and total stroke).

In every region and through the whole analysis period, high blood pressure was the leading risk factor for mortality, but the relative importance of other risks varied by region and over time (appendix). In 1980, high blood pressure was followed by either high cholesterol or high glucose for every region and sex, except for women in the Middle East and north Africa, for whom high BMI was the second leading risk factor. By 2010, the relative importance of high cholesterol fell, and its mortality burden was in the third or fourth greatest for every region and sex; blood pressure was followed by either high BMI or high blood glucose, a result of the worldwide rise in excess weight and hyperglycaemia. The increasing importance of high BMI as a risk factor accelerated after 1990.

Overall, 44% (4·7 million of 10·8 million) of deaths attributable to the combined effects of these risk factors in 2010 were from ischaemic heart disease, followed by 30% from stroke, and 11% from diabetes (figure 3). Ischaemic heart disease was the single most dominant cause of death attributable to high cholesterol (92% [1·80 of 1·95] of all deaths attributable to this risk factor), whereas about the same number of deaths caused by ischaemic heart disease and stroke were attributable to high blood pressure. Deaths directly assigned to diabetes accounted for only 46% (1·24 million of 2·66 million) of deaths caused by high blood glucose, with the remainder having ischaemic heart disease, ischaemic stroke, or chronic kidney as the underlying clinical causes of death.

After accounting for multicausality, 63% (CI 59–67) of all deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes among men and 62% (56–67) among women were attributable to the four risk factors together in 2010 (table). In 1980, the population attributable fractions were 67% (62–72) for men and 66% (61–72) for women (detailed results not shown). High blood pressure alone was responsible for more than 40% of deaths caused by these three diseases, high BMI and glucose concentration were each responsible for about 15% of deaths, and cholesterol for more than 10%. Although high cholesterol was responsible for fewer deaths from the combination of cardiovascular diseases, chronic kidney disease, and diabetes in 2010 compared to the other three risk factors, it caused the second most deaths caused by ischaemic heart disease, about twice that of high glucose. High BMI and glucose were responsible for fewer deaths caused by ischaemic heart disease than was high cholesterol, but were also associated with deaths from haemorrhagic stroke, diabetes, and chronic kidney disease, none of which are affected by high cholesterol. The combined population attributable fraction of the four risk factors together was about three quarters for hypertensive heart disease, about two thirds for ischaemic heart disease, and just more than a half for stroke and chronic kidney disease. The population attributable fraction for the effects of all four risk factors combined increased by only 1 percentage point when we introduced a pairwise correlation between

	Number of deaths (95% CI; thousands)	PAF of risk factor (95% CI)				
		High blood pressure	High BMI	High blood glucose	High serum cholesterol	Four risk factors combined
Men						
All CVDs, diabetes, and CKD	8716 (8291–9201)	46% (42–51)	13% (12–15)	15% (13–18)	10% (8–13)	63% (59–67)
Hypertensive heart disease	387 (325–467)	76% (71–80)	24% (17–30)	0%	0%	76% (71–80)
Ischaemic heart disease	3705 (3341–3951)	48% (39–56)	16% (14–18)	12% (9–17)	23% (17–28)	67% (60–73)
Total stroke	2816 (2516–3226)	53% (46–59)	8% (7–10)	8% (6–11)	2% (1–6)	58% (52–65)
Haemorrhagic and other non-ischaemic stroke	1585 (1263–1952)	57% (49–66)	7% (5–9)	..	0%	61% (53–70)
Ischaemic stroke	1221 (1114–1593)	48% (40–55)	10% (8–12)	..	5% (3–13)	54% (46–63)
Other CVDs	891 (822–964)	37% (33–40)	0%	0%	0%	37% (33–40)
Diabetes	569 (409–603)	0%	27% (11–43)	100%	0%	100%
Chronic kidney disease	357 (298–393)	45% (39–50)	24% (19–29)	23% (19–28)	0%	57% (52–62)
Women						
All CVDs, diabetes, and CKD	8568 (8142–9005)	43% (35–49)	15% (12–17)	15% (13–18)	12% (8–17)	62% (56–67)
Hypertensive heart disease	469 (328–668)	75% (70–80)	28% (19–38)	0%	0%	75% (70–80)
Ischaemic heart disease	3263 (3063–3455)	45% (28–57)	17% (13–21)	11% (8–15)	29% (19–39)	69% (57–76)
Total stroke	2995 (2708–3246)	47% (38–55)	10% (8–12)	7% (5–10)	2% (1–12)	52% (44–62)
Haemorrhagic and other non-ischaemic stroke	1439 (1205–1589)	52% (41–64)	10% (8–12)	..	0%	56% (46–68)
Ischaemic stroke	1559 (1476–1719)	42% (29–52)	9% (7–13)	..	4% (2–22)	49% (35–62)
Other CVDs	860 (807–905)	33% (27–37)	0%	0%	0%	33% (27–37)
Diabetes	667 (513–696)	0%	33% (14–51)	100%	0%	100%
Chronic kidney disease	345 (236–392)	46% (39–52)	29% (24–35)	23% (19–28)	0%	58% (53–63)

CVD=cardiovascular disease. CKD=chronic kidney disease. PAF=population attributable fraction.

Table: **Proportion of deaths attributable to the individual and combined effects of high BMI, blood pressure, blood glucose, and serum total cholesterol in 2010**

See Online for appendix

risk factors in two different sensitivity analyses (with empirical and low *vs* high correlation; data not shown).

At the country level (figure 4), the proportion of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes that were attributable to the combined effect of the four risk factors was lowest in Japan (<50%), followed by some other Asian countries (eg, Cambodia and South Korea), some western European countries, Canada, and Peru; it was highest in the Pacific islands and in some countries in the Middle East, such as Bahrain and Qatar, reaching 80% or more in Marshall Islands, Fiji, and Kiribati. The population attributable fraction for risk factors tended to be low or high for both men and women in the same country (correlation coefficient between population attributable fractions for the two sexes was 0·81).

The geographical patterns of population attributable fractions for individual risk factors differed from their combined effect. High blood pressure was responsible for more than 55% of deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes in central Asia, eastern Europe, and sub-Saharan Africa. By contrast, it was responsible for a third or less of such deaths in some high-income countries—including Canada, Switzerland, South Korea, USA, and Taiwan—in Mexico, and in Papua New Guinea and a few other Pacific islands. Some of the countries with relatively low population attributable fraction for high blood pressure—including Pacific islands and Mexico—were disproportionately affected by high BMI, as were some Middle Eastern countries and South Africa, with population attributable fractions surpassing a third. High BMI was responsible for 5% or less of deaths from cardiovascular diseases, chronic kidney disease, and diabetes in some south and southeast Asian countries (eg, Vietnam, Bangladesh, Nepal, Cambodia, and India), Japan, and a few African countries, such as Ethiopia, DR Congo, Eritrea, and Burkina Faso. The largest population attributable fractions for high blood glucose occurred in the Pacific islands, Mexico, a few Caribbean countries (eg, Trinidad and Tobago and Barbados), and some Middle Eastern countries (eg, Bahrain, Qatar, and Jordan). For example, in Samoa, Kiribati, and Marshall Islands, one half or more of deaths from cardiovascular diseases, chronic kidney disease, and diabetes were attributable to high blood glucose alone. Finally, the proportion of deaths attributable to high serum cholesterol ranged from less than 5% in much of sub-Saharan Africa, Vietnam, and Bangladesh to 20% or more in central and northern

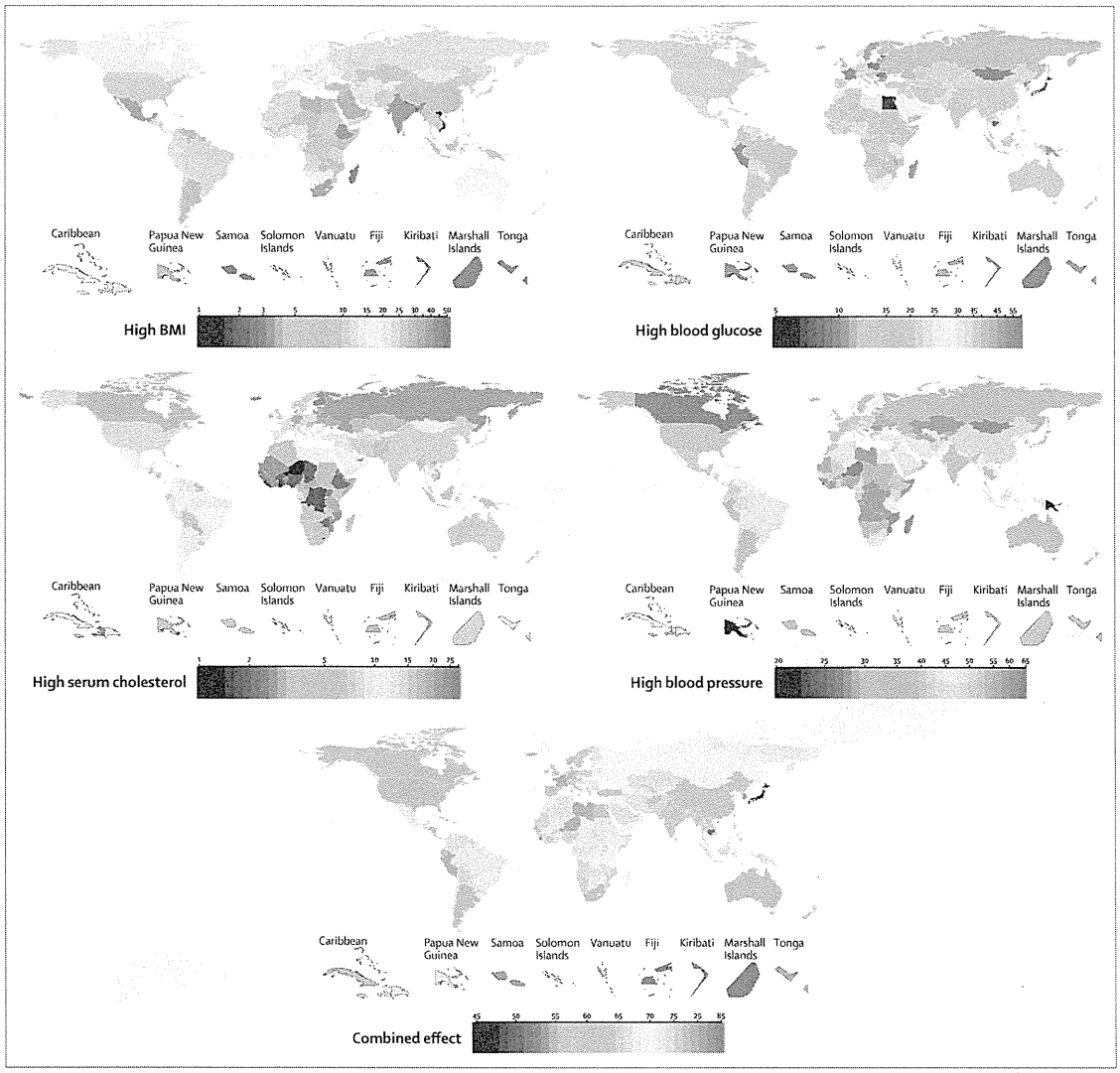

Figure 4: **Proportion of deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to individual and combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol in 2010**
Note that the scales differ by panel.

Europe (Iceland, Finland, Belarus, Russia, Denmark, Lithuania, Russia, Estonia, and Germany) and wealthier Middle Eastern countries such as Kuwait and United Arab Emirates.

In 2010, age-standardised death rates attributable to these four risk factors were highest in countries in central Asia and eastern Europe (figure 5), where population attributable fractions were large (because of high exposure) and mortality from cardiovascular diseases was high. For example, these four risk factors together were responsible for more than 925 deaths from cardiovascular diseases, chronic kidney disease, and diabetes per 100 000 men in Belarus, Mongolia, and Kazakhstan. The attributable death rates were lowest in high-income countries—Japan, Singapore, South Korea, France, Spain, the Netherlands, Australia, and Canada all had fewer than 130 deaths per 100 000 women and fewer than 200 deaths per 100 000 men. These countries had low adult mortality and low population attributable fractions because some metabolic factors are low compared with in other countries. Attributable death rates were also low in Senegal, Peru, Niger, and The Gambia, where death rates from non-communicable diseases were low because these countries are still in the early phases of the demographic and epidemiological transition. From 1980 to 2010, age-standardised death rates attributable to the combined effects of these risk factors decreased in more than 120 countries, especially

Figure 5: **Age-standardised death rates from cardiovascular diseases, diabetes, and chronic kidney disease attributable to combined effects of high BMI, blood pressure, blood glucose, and serum cholesterol by sex in 2010**
Results are not shown for women in Afghanistan because despite relatively low population attributable fractions (figure 4), they had the highest worldwide death rates attributable to these risk factors. This occurred because of very high cardiovascular death rates in the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study. The appendix shows results for women in Afghanistan.

in high-income countries (data not shown). Although some of this decrease was caused by falling population attributable fractions (eg, because of declining trends for systolic blood pressure), the main driver was a decrease in overall cardiovascular disease mortality.

62% of all deaths attributable to the combined effects of these four risk factors in 2010 occurred in ten countries, led by China, India, Russia, and USA (figure 6), because they had large populations or high age-standardised death rates, or both. These four

countries also accounted for the most deaths attributable to each individual risk factor, with the exception of the mortality burden of high BMI, for which India had the eighth highest burden. Over time, middle-income countries such as Mexico, Turkey, Egypt, and Indonesia have replaced high-income European countries such as the UK and France as places where a large number of deaths are attributable to these risk factors (figure 6).

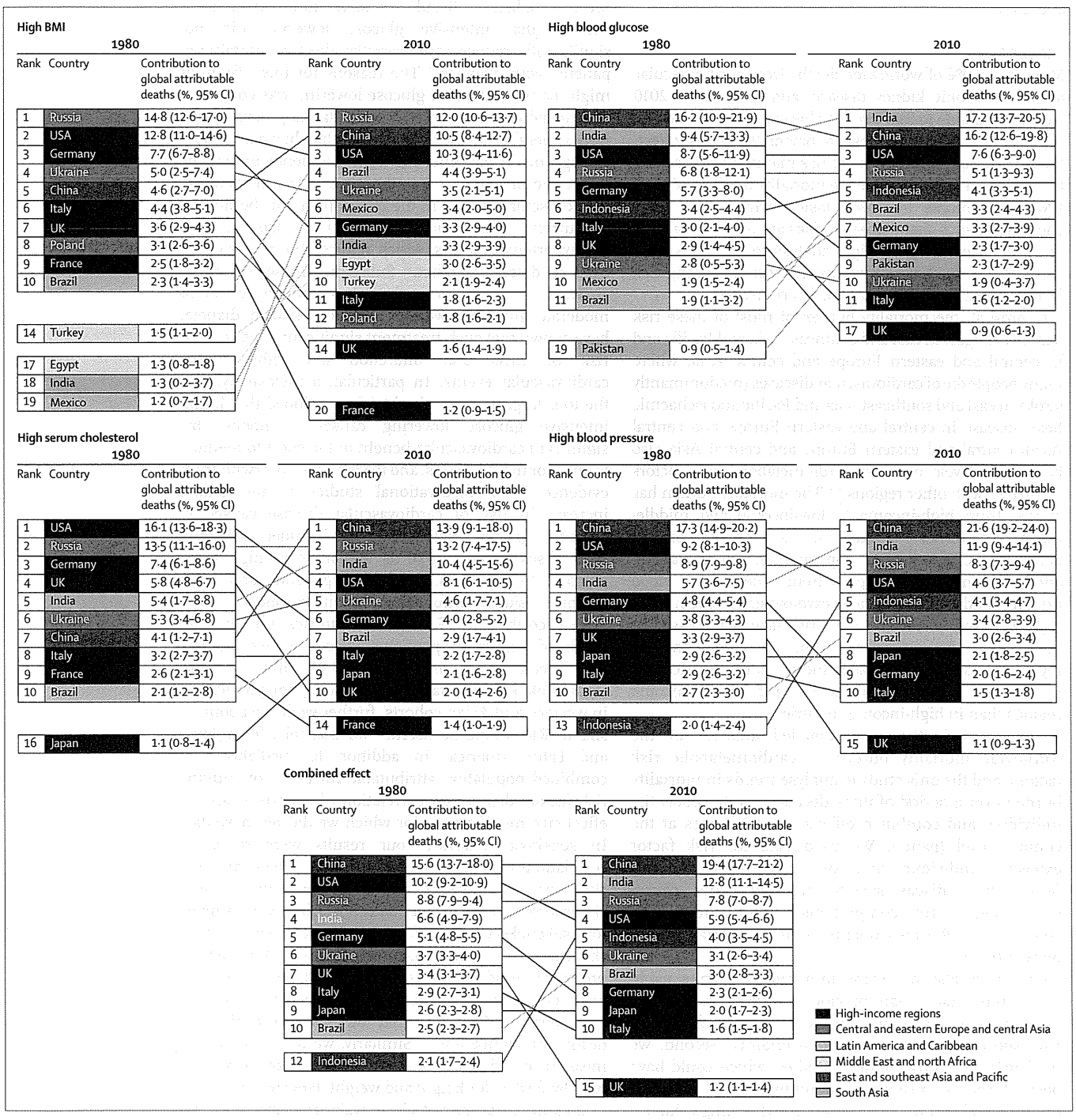

Figure 6: **Ten countries with most deaths from cardiovascular diseases, diabetes, and chronic kidney disease attributable to high BMI, blood pressure, serum cholesterol, and blood glucose in 1980 and 2010**