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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost minimization analysis using Gamma regression models

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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost minimization analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat to a population health. This detrimental effect also increases medical expenses, especially for the elderly population. The present age-specific investigation into medical expenditure, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost minimization analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 39,114 participants aged 40 years and over.

Main outcome measures Mean annual medical expenditure.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects annual medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure>140 mmHg or diastolic blood pressure>90 mmHg), hypercholesterolemia (serum total cholesterol>240 mg/dl), high blood glucose (casual blood glucose>200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were

carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean annual medical expenditure for the no CVD risk factor group was only 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but this expenditure was seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 10.2%, women: 9.3%) than for the elderly (men: -0.7%, women: 4.7%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion A high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost minimization analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also increases medical expenses.

> The present study examined how age- and sex-specific trends influence total medical expenditure and assessed how the clustering of CVD risk factors affects the Japanese population.

Key Messages

>The total overspend of annual medical expenditure is larger for the non-elderly than for the elderly in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors as opposed to those with three or four risk factors, except for elderly men.

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown

that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost minimization analysis using Gamma regression models, especially for the elderly population. The present study thus examines how age- and sex-specific trends influence total medical expenditure and assesses how the clustering of CVD risk factors affects the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we calculated mean annual medical expenditure as the sum of monthly medical expenditure divided by the total periods of

observation. The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis (n=31,119). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four

categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

Because data on individual medical expenses differed by the period of subscription to the NHI, individual medical expenses were divided by these periods of subscription and expressed as the mean expenses per year of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean annual medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a substantial proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific annual medical expenditure for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean annual medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated annual medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated annual medical expenditure for each CVD risk

factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean annual medical expenditure for the no CVD risk factor group is just 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but that this expenditure is seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean annual medical expenditure for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted annual medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in elderly women (cost ratio: 1.74). The total overspend was larger in the non-elderly population (men: 10.2%, women: 9.3%) than it was in the elderly (men: -0.7%, women: 4.7%). The total overspend was mostly driven by the groups with one (non-elderly men: 3.6%, non-elderly women: 4.9%, elderly women: 3.0%) or two risk factors (non-elderly men: 5.4%, non-elderly women: 4.1%, elderly women: 1.4%) compared with three or four risk factors (non-elderly men: 1.2%, non-elderly women: 0.3%, elderly women: 0.3%), with the exception of elderly men.

Discussion

We performed a community-based cost minimization analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures

(statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. We applied a Gamma regression model[12–15] for the cost minimization analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for 9% of total medical expenditure when the one and two CVD risk factor groups were combined compared with 4.4% for elderly women and -0.7% for elderly men. However, it is difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk

factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. First, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. Finally, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable. Thus, further studies are required to clarify the effects of these variables.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4890; women:11,737			Men:6892, women:10,520			Men:2337, women:2362			Men:262, women:114		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	11	-	68	11	-	67	10	-	65	10	-
Systolic blood pressur	123	11	0	138	19	54	148	17	87	151	14	96
Total choresterol	187	28	0	191	31	5	201	41	23	231	41	65
Blood glucose	104	24	0	107	30	1	118	51	8	187	95	49
Current smokers	-	-	0	-	-	39	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	10	-	66	10	-
Systolic blood pressur	122	12	0	143	18	70	150	16	92	155	15	100
Total choresterol	199	25	0	214	34	23	248	33	80	260	28	91
Blood glucose	98	19	0	102	27	1	114	50	8	174	93	44
Current smokers	-	-	0	-	-	7	-	-	20	-	-	68

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

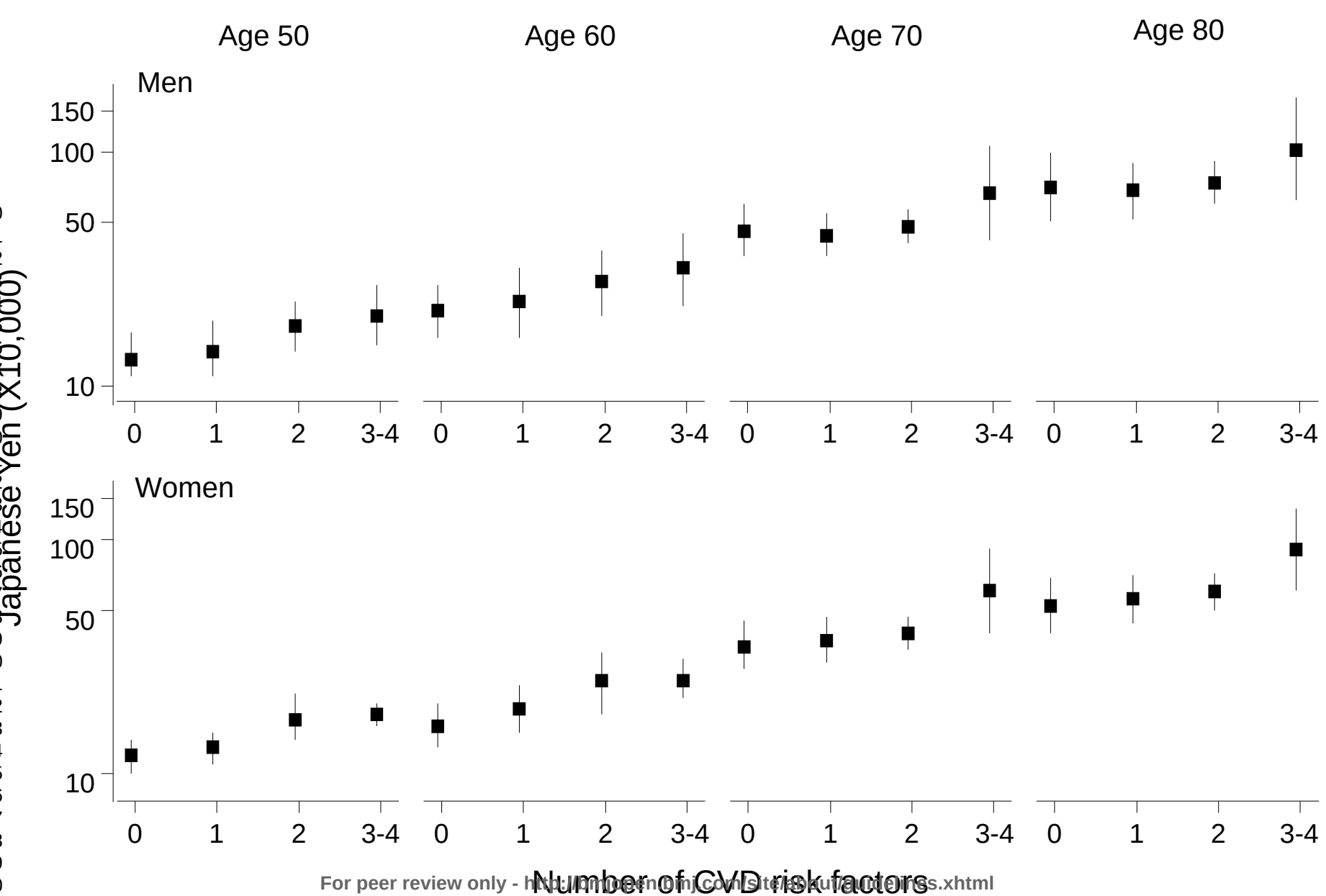
Figure 1. The age- and sex-specific estimated annual medical expenditure by CVD risk factor group.

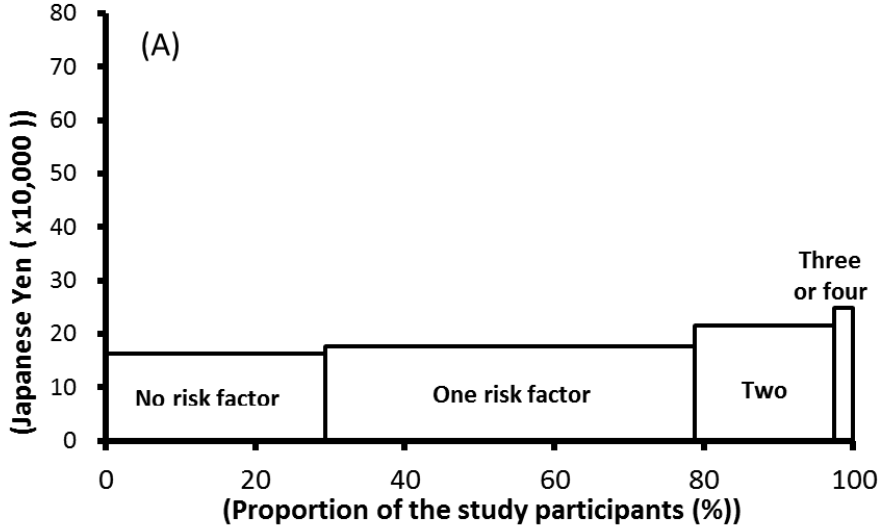
The black rectangles show the annual medical expenditure of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean annual medical expenditure, and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

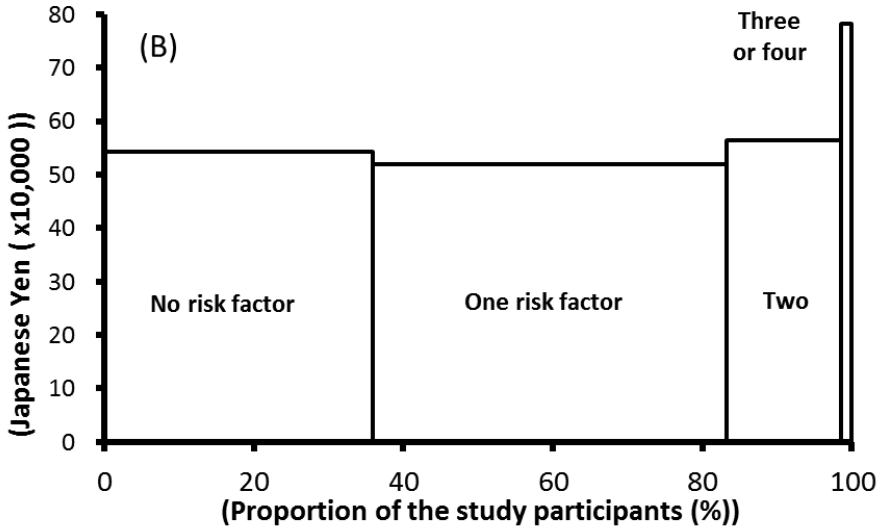
The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Fig 1

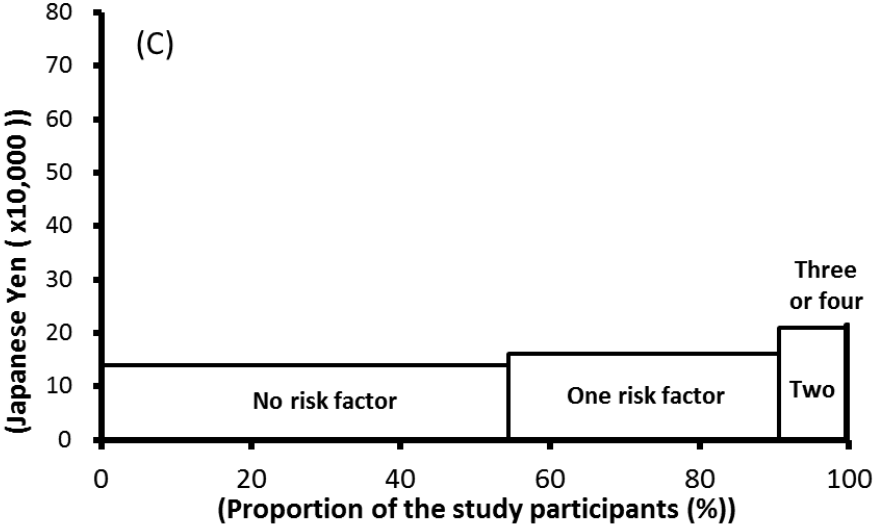




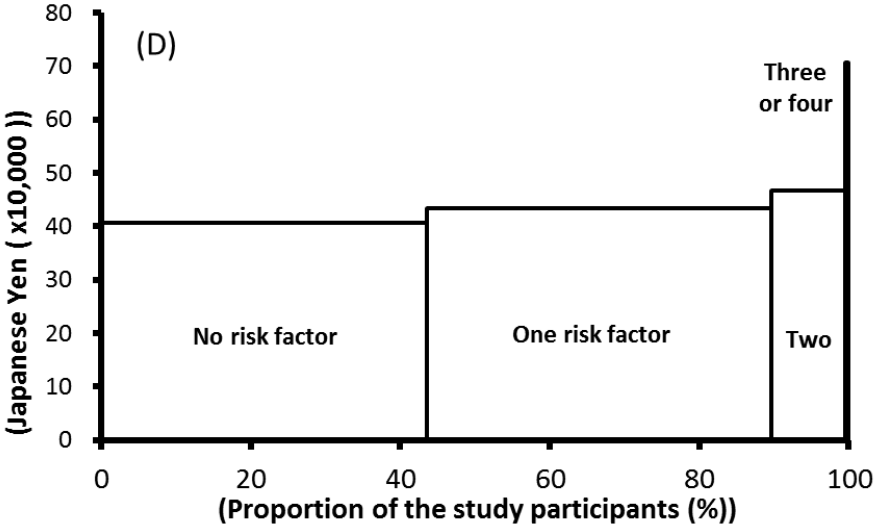
Ratio	1.0 (reference)	1.07	1.32	1.52
Excess fraction (%)		3.6	5.4	1.2



Ratio	1.0 (reference)	0.96	1.04	1.44
Excess fraction (%)		-2.0	0.6	0.7



Ratio	1.0 (reference)	1.15	1.51	1.54
Excess fraction (%)		4.9	4.1	0.3



Ratio	1.0 (reference)	1.07	1.15	1.74
Excess fraction (%)		3.0	1.4	0.3

Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction and Methods	
(5) The alternatives being compared are clearly described	Introduction and Methods	
(6) The form of economic evaluation used is stated	Introduction and Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction and Methods	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	Methods	
(27) The approach to sensitivity analysis is given	N/A	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	N/A	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table and Figures	
(33) The answer to the study question is given	Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost minimization analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat to a population health. This detrimental effect also increases medical expenses, especially for the elderly population. The age-specific quantitative assessment of the medical expenditure, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost minimization analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 39,114 participants aged 40 years and over.

Main outcome measures Mean medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean medical expenditure (per year) for the no CVD risk factor group was only 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but this expenditure was seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 10.2%, women: 9.3%) than for the elderly (men: -0.7%, women: 4.7%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion Our quantitative assessments showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost minimization analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also increases medical expenses.

> The present study examined how age- and sex-specific trends influence total medical expenditure and assessed how the clustering of CVD risk factors affects the Japanese population.

Key Messages

>The total overspend of annual medical expenditure is larger for the non-elderly than for the elderly in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors as opposed to those with three or four risk factors, except for elderly men.

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown

that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost minimization analysis using Gamma regression models, especially for the elderly population. The present study thus conducted the age- and sex-specific quantitative assessments of total medical expenditure and examines how the clustering of CVD risk factors affects the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we used a mean medical expenditure (per year), which was calculated by summing all medical expenditure throughout the

observation periods and divided by the total observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis (n=31,119). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg),

hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

Because data on individual medical expenses differed by the period of subscription to the NHI, individual medical expenses were divided by these periods of subscription and expressed as the mean expenses per year of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional

variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated mean medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women

followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean medical expenditure (per year) for the no CVD risk factor group is just 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but that this expenditure is seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted mean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in elderly women (cost ratio: 1.74). The total overspend was larger in the non-elderly population (men: 10.2%, women: 9.3%) than it was in the elderly (men: -0.7%, women: 4.7%). The total overspend was mostly driven by the groups with one (non-elderly men: 3.6%, non-elderly women: 4.9%, elderly women: 3.0%) or two risk factors (non-elderly men: 5.4%, non-elderly women: 4.1%, elderly women: 1.4%) compared with three or four risk factors

(non-elderly men: 1.2%, non-elderly women: 0.3%, elderly women: 0.3%), with the exception of elderly men.

Discussion

We performed a community-based cost minimization analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the

insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost minimization analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they

can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for 9% of total medical expenditure when the one and two CVD risk factor groups were combined compared with 4.4% for elderly women and -0.7% for elderly men. However, it is difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess

medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4890; women:11,737			Men:6892, women:10,520			Men:2337, women:2362			Men:262, women:114		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	11	-	68	11	-	67	10	-	65	10	-
Systolic blood pressur	123	11	0	138	19	54	148	17	87	151	14	96
Total choresterol	187	28	0	191	31	5	201	41	23	231	41	65
Blood glucose	104	24	0	107	30	1	118	51	8	187	95	49
Current smokers	-	-	0	-	-	39	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	10	-	66	10	-
Systolic blood pressur	122	12	0	143	18	70	150	16	92	155	15	100
Total choresterol	199	25	0	214	34	23	248	33	80	260	28	91
Blood glucose	98	19	0	102	27	1	114	50	8	174	93	44
Current smokers	-	-	0	-	-	7	-	-	20	-	-	68

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

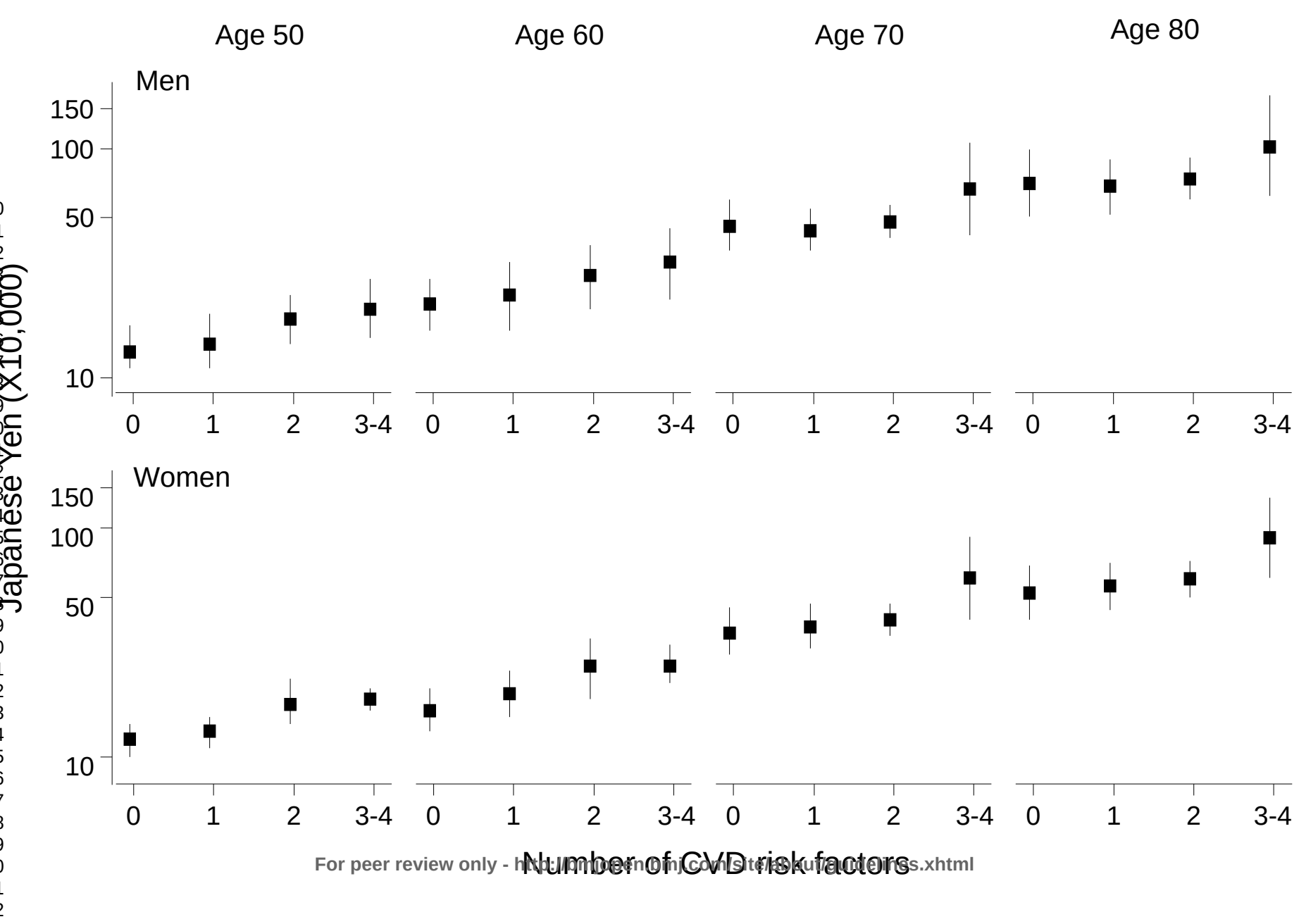
Figure 1. The age- and sex-specific estimated mean medical expenditure (per year) by CVD risk factor group.

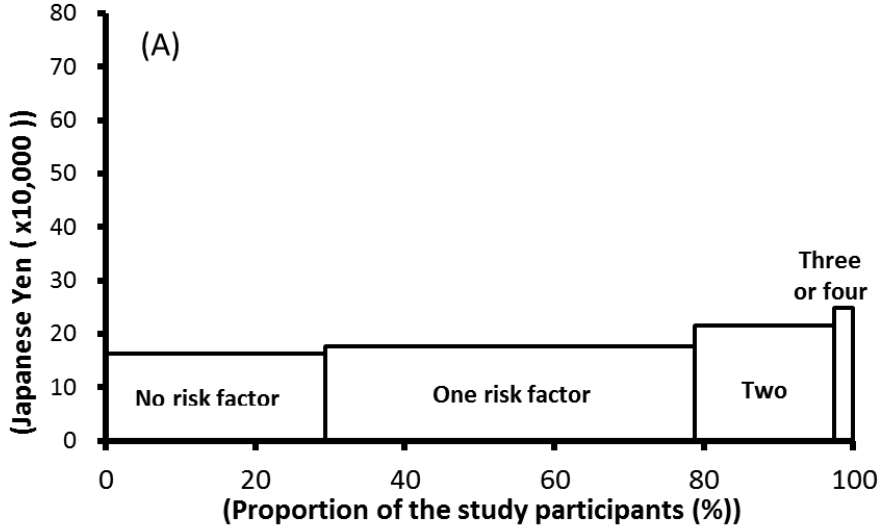
The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean medical expenditure (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

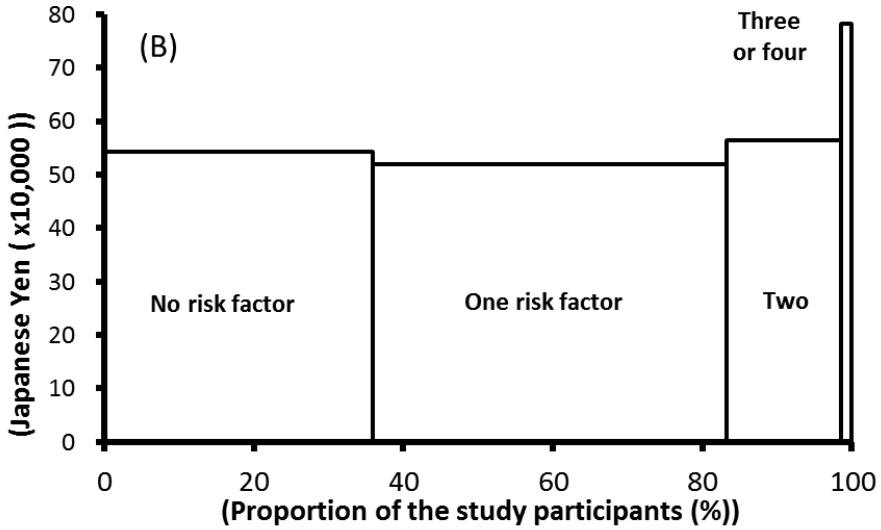
The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Fig 1

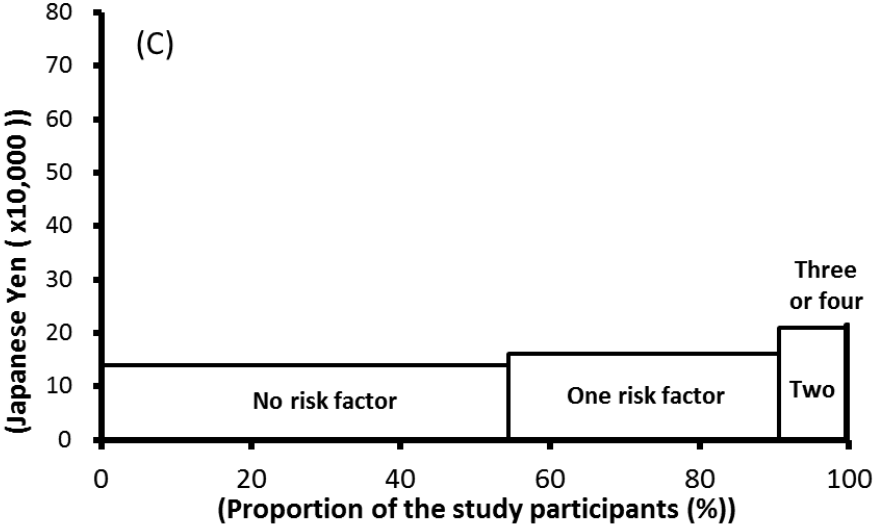




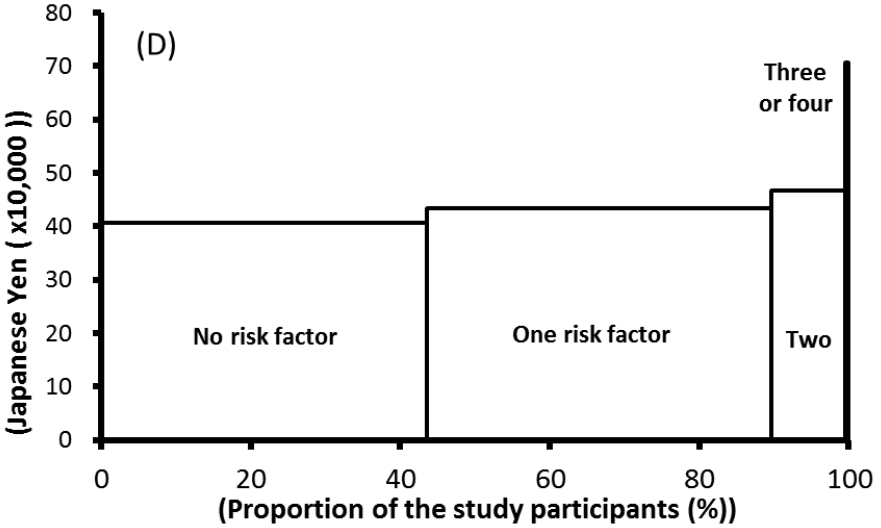
Ratio	1.0 (reference)	1.07	1.32	1.52
Excess fraction (%)		3.6	5.4	1.2



Ratio	1.0 (reference)	0.96	1.04	1.44
Excess fraction (%)		-2.0	0.6	0.7



Ratio	1.0 (reference)	1.15	1.51	1.54
Excess fraction (%)		4.9	4.1	0.3



Ratio	1.0 (reference)	1.07	1.15	1.74
Excess fraction (%)		3.0	1.4	0.3

Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction and Methods	
(5) The alternatives being compared are clearly described	Introduction and Methods	
(6) The form of economic evaluation used is stated	Introduction and Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction and Methods	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	Methods	
(27) The approach to sensitivity analysis is given	N/A	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	N/A	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table and Figures	
(33) The answer to the study question is given	Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat to a population health. This detrimental effect also increases medical expenses, especially for the elderly population. The ~~present~~ age-specific ~~investigation into~~quantitative assessment of the medical expenditure, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost minimization analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 39,114 participants aged 40 years and over.

Main outcome measures Mean ~~annual~~ medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects ~~annual~~mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were

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carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group was only 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but this expenditure was seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 10.2%, women: 9.3%) than for the elderly (men: -0.7%, women: 4.7%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion ~~A~~Our quantitative assessments showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost minimization analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also increases medical expenses.

> The present study examined how age- and sex-specific trends influence total medical expenditure

and assessed how the clustering of CVD risk factors affects the Japanese population.

Key Messages

>The total overspend of annual medical expenditure is larger for the non-elderly than for the elderly in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors as opposed to those with three or four risk factors, except for elderly men.

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these

risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost minimization analysis using Gamma regression models, especially for the elderly population. The present study thus ~~examines how~~conducted the age- and sex-specific ~~trends influence~~quantitative assessments of total medical expenditure and ~~assesses~~examines how the clustering of CVD risk factors affects the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides

data from April 2000 to March 2006. For the economic evaluation, we ~~calculated~~used a mean ~~annual~~ medical expenditure ~~as the sum of monthly~~(per year), which was calculated by summing all medical expenditure throughout the observation periods and divided by the total ~~periods of observation.~~observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis (n=31,119). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

Because data on individual medical expenses differed by the period of subscription to the NHI, individual medical expenses were divided by these periods of subscription and expressed as the mean expenses per year of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean ~~annual~~ medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a ~~substantial~~certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific ~~annual~~ medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean ~~annual~~ medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated ~~annual~~mean medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the

number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated ~~annual~~mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group is just 130,000 Yen at age 50 (men: 133,413 Yen, women: 115,470 Yen), but that this expenditure is seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974,449 Yen, women: 906,821 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean ~~annual~~ medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted ~~annual~~mean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in elderly women (cost ratio: 1.74). The total

overspend was larger in the non-elderly population (men: 10.2%, women: 9.3%) than it was in the elderly (men: -0.7%, women: 4.7%). The total overspend was mostly driven by the groups with one (non-elderly men: 3.6%, non-elderly women: 4.9%, elderly women: 3.0%) or two risk factors (non-elderly men: 5.4%, non-elderly women: 4.1%, elderly women: 1.4%) compared with three or four risk factors (non-elderly men: 1.2%, non-elderly women: 0.3%, elderly women: 0.3%), with the exception of elderly men.

Discussion

We performed a community-based cost minimization analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the

community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost minimization analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for 9% of total medical expenditure when the one and two CVD risk factor groups were combined compared with 4.4% for elderly women and -0.7% for elderly men. However, it is difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. ~~First, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.~~First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment

status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. ~~Finally, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable. Thus, further studies are required to clarify the effects of these variables~~Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both

necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4890; women:11,737			Men:6892, women:10,520			Men:2337, women:2362			Men:262, women:114		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	11	-	68	11	-	67	10	-	65	10	-
Systolic blood pressur	123	11	0	138	19	54	148	17	87	151	14	96
Total choresterol	187	28	0	191	31	5	201	41	23	231	41	65
Blood glucose	104	24	0	107	30	1	118	51	8	187	95	49
Current smokers	-	-	0	-	-	39	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	10	-	66	10	-
Systolic blood pressur	122	12	0	143	18	70	150	16	92	155	15	100
Total choresterol	199	25	0	214	34	23	248	33	80	260	28	91
Blood glucose	98	19	0	102	27	1	114	50	8	174	93	44
Current smokers	-	-	0	-	-	7	-	-	20	-	-	68

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

Figure 1. The age- and sex-specific estimated ~~annual~~mean medical expenditure (per year) by CVD risk factor group.

The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the ~~annual~~mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean ~~annual~~ medical expenditure~~,~~ (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat for increasing medical expenses. The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 33,213 participants aged 40 years and over

Main outcome measures Mean medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean medical expenditure (per year) for the no CVD risk factor group was only 110,000 Yen at age 50 (men: 110,708 Yen, women: 107,109 Yen), but this expenditure was six to

seven times higher for 80-year-olds who have three or four CVD risk factors (men:603,351 Yen, women: 765,673 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 15.4%, women: 11.1%) than for the elderly (men: 0.1%, women: 5.2%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also increases medical expenses.

> The present study examined how age- and sex-specific trends influence total medical expenditure and assessed how the clustering of CVD risk factors affects the Japanese population.

Key Messages

>The total overspend of annual medical expenditure is larger for the non-elderly than for the elderly

in Japan.

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Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their

combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost analysis using Gamma regression models, especially for the elderly population. The present study examined the age- and sex-specific proportion and distribution of medical expenditure attributable for the number of CVD risk factors in the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance

institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we used a mean medical expenditure (per year), which was calculated by summing all medical expenditure throughout the observation periods and divided by the total observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an

annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis. The participants who have not censored during whole follow-up period were included in the analysis (n=33,213). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and

smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each

CVD risk factor group. The cost ratio represents the estimated mean medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean medical expenditure (per year) for the no CVD risk factor group is just 110,000 Yen at age 50 (men: 110,708 Yen, women: 107,109 Yen), but that this expenditure is sex to seven times

higher for 80-year-olds who have three or four CVD risk factors (men: 603,351 Yen, women: 765,673 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted mean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in non-elderly men (cost ratio: 1.86). The total overspend was larger in the non-elderly population (men: 15.4%, women: 11.1%) than it was in the elderly (men: 0.1%, women: 5.2%). The total overspend was mostly driven by the groups with one (non-elderly men: 6.8%, non-elderly women: 7.4%, elderly women: 3.7%) or two risk factors (non-elderly men: 6.8%, non-elderly women: 3.5%, elderly women: 1.3%) compared with three or four risk factors (non-elderly men: 1.8%, non-elderly women: 0.2%, elderly women: 0.2%), with the exception of elderly men.

Discussion

We performed a community-based cost analysis to investigate the sex- and age-specific

effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using

this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost minimization analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for more thqn 10% of total medical expenditure when the one and two CVD risk factor groups were combined compared with 5.0% for elderly women and 0.0% for elderly men. However, it is difficult to

implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD

risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H20-Junkankitou [Seishuu]-Ippan-013 and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H23-Junkankitou [Seishuu]-Ippan-005).

Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4187; women:9924			Men:5947, women:8953			Men1945, women:1964			Men:206, women:87		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	10	-	68	11	-	67	10	-	65	10	-
Systolic blood pressure	124	11	0	138	19	55	148	17	87	151	15	96
Total choresterol	188	27	0	191	31	5	202	41	23	234	39	68
Blood glucose	103	23	0	106	29	1	118	50	8	178	94	45
Current smokers	-	-	0	-	-	38	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	9	-	66	9	-
Systolic blood pressure	122	12	0	143	18	70	150	15	93	156	15	100
Total choresterol	200	24	0	214	34	23	249	32	82	261	23	94
Blood glucose	98	19	0	102	27	1	112	46	7	168	92	39
Current smokers	-	-	0	-	-	6	-	-	18	-	-	70

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

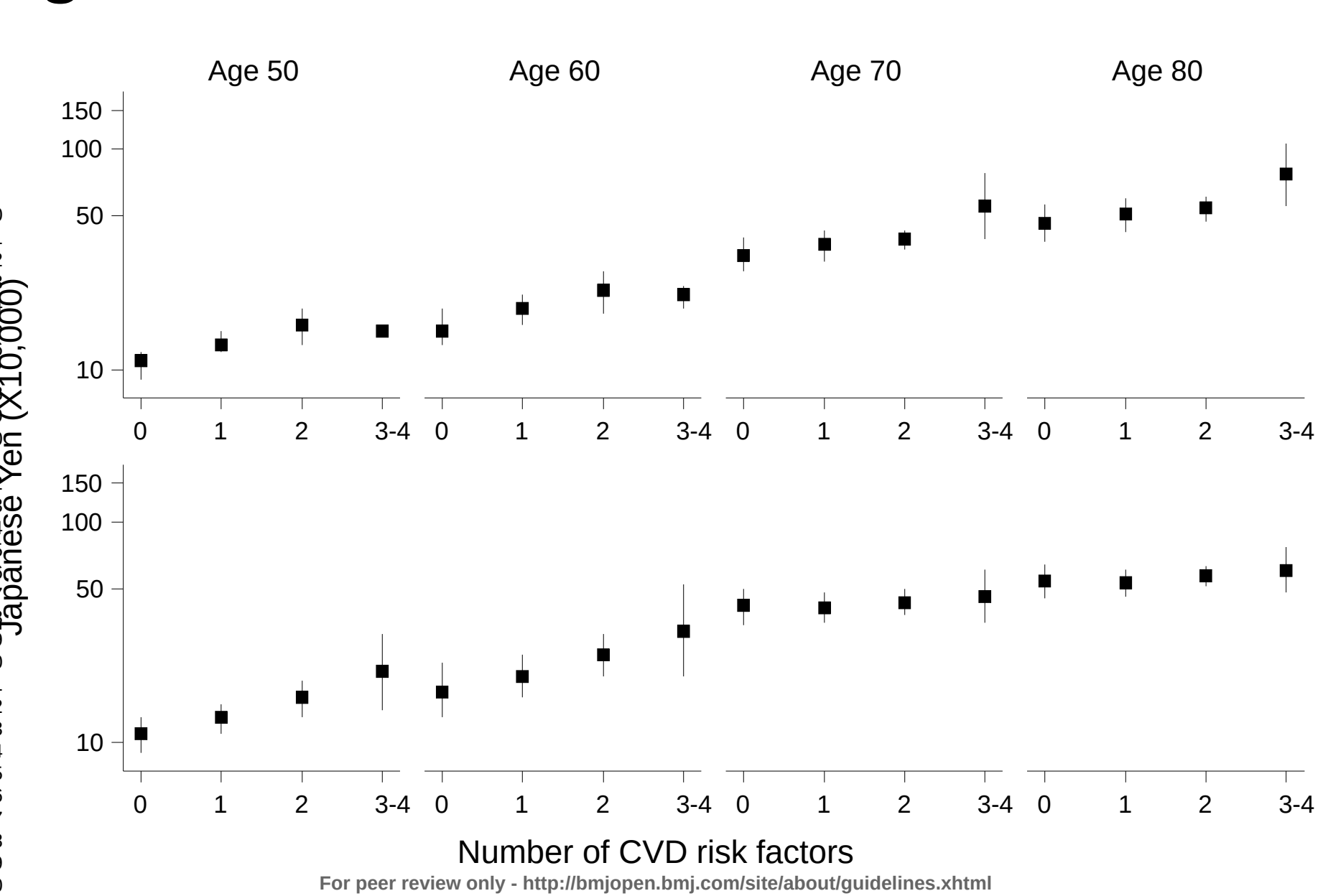
Figure 1. The age- and sex-specific estimated mean medical expenditure (per year) by CVD risk factor group.

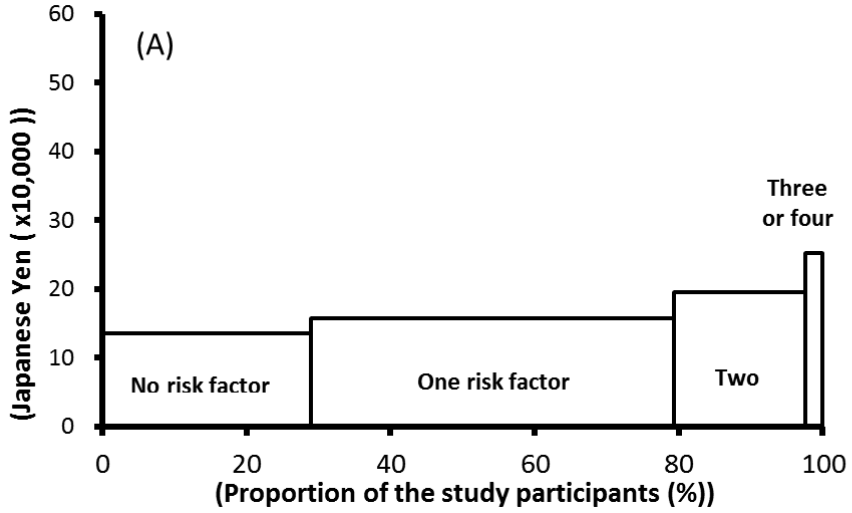
The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean medical expenditure (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

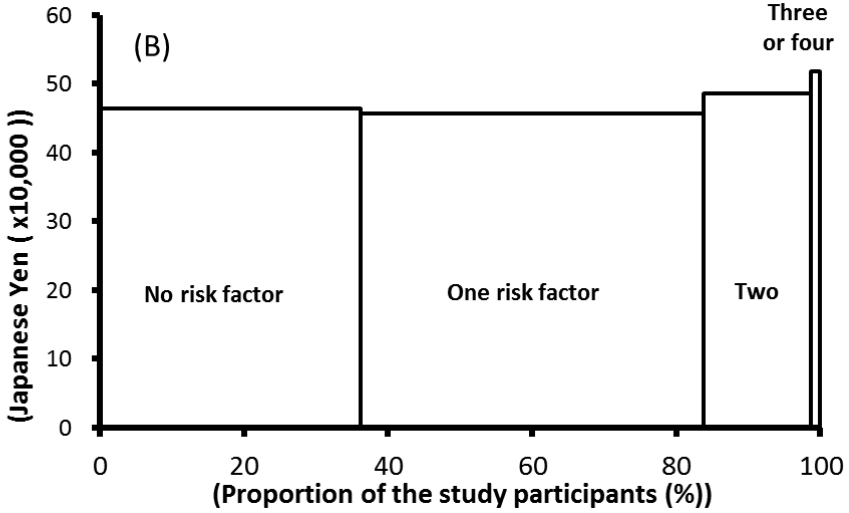
The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Fig. 1

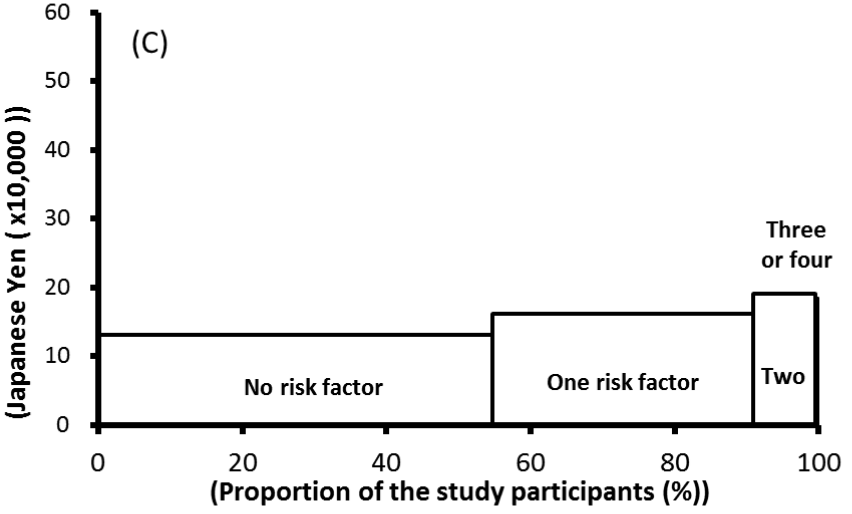

Age 50
Age 60
Age 70
Age 80
150
100
50
10
0
1
2
3-4
Japanese Yen (X10,000)
Number of CVD risk factors



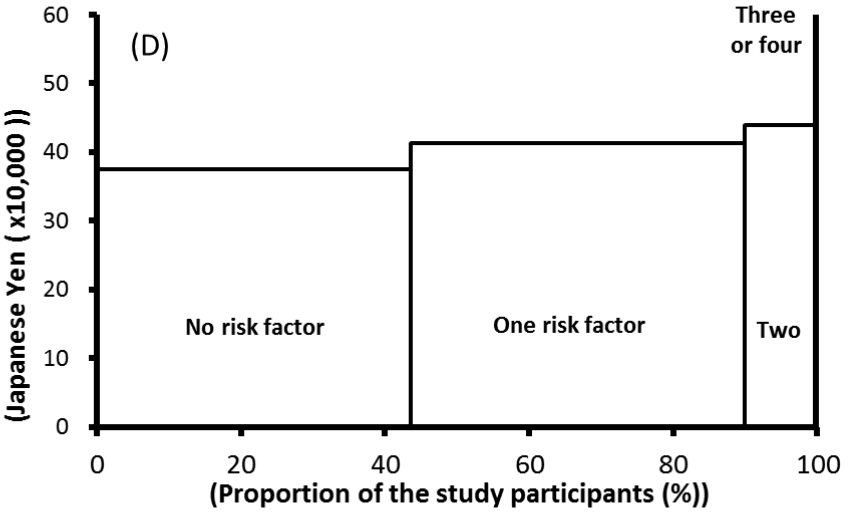
Ratio	1.0 (reference)	1.16	1.44	1.86
Excess fraction (%)		6.8	6.8	1.8



Ratio	1.0 (reference)	0.99	1.05	1.12
Excess fraction (%)		-0.6	0.6	0.1



Ratio	1.0 (reference)	1.23	1.46	1.40
Excess fraction (%)		7.4	3.5	0.2



Ratio	1.0 (reference)	1.10	1.17	1.66
Excess fraction (%)		3.7	1.3	0.2

The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost ~~minimization~~ analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat ~~to a population health. This detrimental effect also~~for increasinges medical expenses~~, especially for the elderly population.~~ The ~~present~~ age-specific ~~investigation into~~quantitative assessment ~~of~~ ~~the~~proportion and distribution of medical expenditure attributable to CVD risk factors, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost ~~minimization~~ analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 3~~9~~,213~~14~~ participants aged 40 years and over.

Main outcome measures Mean ~~annual~~ medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects ~~annual~~mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual

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blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group was only 113~~3~~0,000 Yen at age 50 (men: 11033~~,708413~~ Yen, women: 10715~~,109470~~ Yen), but this expenditure was six to seven times higher for 80-year-olds who have three or four CVD risk factors (men: ~~974~~603,351~~449~~ Yen, women: ~~906,821~~765,673 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 150.~~42~~%, women: 119.~~13~~%) than for the elderly (men: -0.~~17~~%, women: 54.~~27~~%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion ~~AOur~~ The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors~~quantitative assessments~~ showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost ~~minimization~~ analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also

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increases medical expenses.

> The present study examined how age- and sex-specific trends influence total medical expenditure and assessed how the clustering of CVD risk factors affects the Japanese population.

Key Messages

>The total overspend of annual medical expenditure is larger for the non-elderly than for the elderly in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors as opposed to those with three or four risk factors, except for elderly men.

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for

cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost ~~minimization~~ analysis using Gamma regression models, especially for the elderly population. The present study ~~thus examines how conducted~~examined the age- and sex-specific proportion and

distribution of medical expenditure attributable for the number of CVD risk factors ~~trends influencequantitative assessments of total medical expenditure and assessesexamines how the clustering of CVD risk factors affects~~in the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga

prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we ~~calculated~~used a mean ~~annual~~ medical expenditure ~~as the sum of monthly~~(per year), which was calculated by summing all medical expenditure throughout the observation periods and divided by the total ~~periods of observation.~~observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood

glucose, and smoking habits (see next subsection) were included in the analysis. The participants who have not censored during whole follow-up period were included in the analysis (n=331,211139).

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

~~Because data on individual medical expenses differed by the period of subscription to the NHI, individual medical expenses were divided by these periods of subscription and expressed as the mean expenses per year of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.~~

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A gamma regression model, which is a member of generalized linear models[12], was used to

estimate the mean ~~annual~~ medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a ~~substantial~~certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific ~~annual~~ medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean ~~annual~~ medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated ~~annual~~mean medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was

performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated ~~annual~~mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group is just 113~~3~~0,000 Yen at age 50 (men: 11033~~,708413~~ Yen, women: 107,109~~15,470~~ Yen), but that this expenditure is sex to seven times higher for 80-year-olds who have three or four CVD risk factors (men: ~~974~~603,351~~,449~~ Yen, women: ~~906,821~~765,673 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean ~~annual~~ medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and

overspends (excess fractions) in each group are also shown by sex and age. The adjusted ~~annual~~mean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in non-elderly men~~elderly women~~ (cost ratio: 1.~~74~~86). The total overspend was larger in the non-elderly population (men: 1~~5~~0.~~42~~%, women: 11~~9~~.1~~3~~%) than it was in the elderly (men: ~~-~~0.1~~7~~%, women: ~~5~~4.~~27~~%). The total overspend was mostly driven by the groups with one (non-elderly men: ~~63~~.86%, non-elderly women: 74.~~49~~%, elderly women: 3.~~70~~%) or two risk factors (non-elderly men: ~~65~~.~~84~~%, non-elderly women: 34.~~51~~%, elderly women: 1.34%) compared with three or four risk factors (non-elderly men: 1.~~82~~%, non-elderly women: 0.~~23~~%, elderly women: 0.~~23~~%), with the exception of elderly men.

Discussion

We performed a community-based cost ~~minimization~~ analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD

risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost

minimization analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for more thqn 109%– of total medical expenditure when the one and two CVD risk factor groups were combined compared with 54.04% for elderly women and -0.07% for elderly men. However, it is difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. ~~First, because the public medical insurance~~

~~system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.~~First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. ~~Finally, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable. Thus, further studies are required to clarify the effects of these variables~~Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors

on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4890; women:11,737			Men:6892, women:10,520			Men:2337, women:2362			Men:262, women:114		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	11	-	68	11	-	67	10	-	65	10	-
Systolic blood pressur	123	11	0	138	19	54	148	17	87	151	14	96
Total choresterol	187	28	0	191	31	5	201	41	23	231	41	65
Blood glucose	104	24	0	107	30	1	118	51	8	187	95	49
Current smokers	-	-	0	-	-	39	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	10	-	66	10	-
Systolic blood pressur	122	12	0	143	18	70	150	16	92	155	15	100
Total choresterol	199	25	0	214	34	23	248	33	80	260	28	91
Blood glucose	98	19	0	102	27	1	114	50	8	174	93	44
Current smokers	-	-	0	-	-	7	-	-	20	-	-	68

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4187; women:9924			Men:5947, women:8953			Men1945, women:1964			Men:206, women:87		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	10	-	68	11	-	67	10	-	65	10	-
Systolic blood pressure	124	11	0	138	19	55	148	17	87	151	15	96
Total choresterol	188	27	0	191	31	5	202	41	23	234	39	68
Blood glucose	103	23	0	106	29	1	118	50	8	178	94	45
Current smokers	-	-	0	-	-	38	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	9	-	66	9	-
Systolic blood pressure	122	12	0	143	18	70	150	15	93	156	15	100
Total choresterol	200	24	0	214	34	23	249	32	82	261	23	94
Blood glucose	98	19	0	102	27	1	112	46	7	168	92	39
Current smokers	-	-	0	-	-	6	-	-	18	-	-	70

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

Figure 1. The age- and sex-specific estimated ~~annual~~mean medical expenditure (per year) by CVD risk factor group.

The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the ~~annual~~mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean ~~annual~~ medical expenditure~~,~~ (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction and Methods	
(5) The alternatives being compared are clearly described	Introduction and Methods	
(6) The form of economic evaluation used is stated	Introduction and Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction and Methods	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	Methods	
(27) The approach to sensitivity analysis is given	N/A	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	N/A	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table and Figures	
(33) The answer to the study question is given	Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost analysis using Gamma regression models

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The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat for increasing medical expenses. The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 33,213 participants aged 40 years and over

Main outcome measures Mean medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean medical expenditure (per year) for the no CVD risk factor group was only 110,000 Yen at age 50 (men: 110,708 Yen, women: 107,109 Yen), but this expenditure was six to

seven times higher for 80-year-olds who have three or four CVD risk factors (men:603,351 Yen, women: 765,673 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 15.4%, women: 11.1%) than for the elderly (men: 0.1%, women: 5.2%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also increases medical expenses.

> The present study examined age and sex specific clustering of cardiovascular risk factors, and how it affected medical expenditure in the Japanese population.

Key Messages

>The total overspends attributable to cardiovascular risk factors is larger among the non-elderly

population in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors rather than by those with three or four, except for men aged 65 and over.

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

> The use of large comprehensive community-based database of health examination and medical expenditure brought us the stratified information by sex and age.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown

that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost analysis using Gamma regression models, especially for the elderly population. The present study examined the age- and sex-specific proportion and distribution of medical expenditure attributable for the number of CVD risk factors in the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we used a mean medical expenditure (per year), which was calculated by summing all medical expenditure throughout the

observation periods and divided by the total observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis. The participants who have not censored during whole follow-up period were included in the analysis (n=33,213). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension

(systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean medical expenditure and the corresponding number of

participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated mean medical expenditure of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows

that the mean medical expenditure (per year) for the no CVD risk factor group is just 110,000 Yen at age 50 (men: 110,708 Yen, women: 107,109 Yen), but that this expenditure is sex to seven times higher for 80-year-olds who have three or four CVD risk factors (men: 603,351 Yen, women: 765,673 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted mean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in non-elderly men (cost ratio: 1.86). The total overspend was larger in the non-elderly population (men: 15.4%, women: 11.1%) than it was in the elderly (men: 0.1%, women: 5.2%). The total overspend was mostly driven by the groups with one (non-elderly men: 6.8%, non-elderly women: 7.4%, elderly women: 3.7%) or two risk factors (non-elderly men: 6.8%, non-elderly women: 3.5%, elderly women: 1.3%) compared with three or four risk factors (non-elderly men: 1.8%, non-elderly women: 0.2%, elderly women: 0.2%), with the exception of elderly men.

Discussion

We performed a community-based cost analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for

analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for more

thqn 10% of total medical expenditure when the one and two CVD risk factor groups were combined compared with 5.0% for elderly women and 0.0% for elderly men. However, it is difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4187; women:9924			Men:5947, women:8953			Men1945, women:1964			Men:206, women:87		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	10	-	68	11	-	67	10	-	65	10	-
Systolic blood pressure	124	11	0	138	19	55	148	17	87	151	15	96
Total choresterol	188	27	0	191	31	5	202	41	23	234	39	68
Blood glucose	103	23	0	106	29	1	118	50	8	178	94	45
Current smokers	-	-	0	-	-	38	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	9	-	66	9	-
Systolic blood pressure	122	12	0	143	18	70	150	15	93	156	15	100
Total choresterol	200	24	0	214	34	23	249	32	82	261	23	94
Blood glucose	98	19	0	102	27	1	112	46	7	168	92	39
Current smokers	-	-	0	-	-	6	-	-	18	-	-	70

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

Figure 1. The age- and sex-specific estimated mean medical expenditure (per year) by CVD risk factor group.

The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean medical expenditure (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction and Methods	
(5) The alternatives being compared are clearly described	Introduction and Methods	
(6) The form of economic evaluation used is stated	Introduction and Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction and Methods	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	Methods	
(27) The approach to sensitivity analysis is given	N/A	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	N/A	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table and Figures	
(33) The answer to the study question is given	Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost ~~minimization~~ analysis using Gamma regression models

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Abstract

Objective The clustering of cardiovascular disease (CVD) risk factors is a serious threat ~~to a population health. This detrimental effect also~~for increasinges medical expenses~~, especially for the elderly population.~~ The ~~present~~ age-specific ~~investigation intoquantitative assessment of~~ ~~the~~proportion and distribution of ~~–~~medical expenditure attributable to CVD risk factors, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Design Cost ~~minimization~~ analysis using individuals' medical expenses and their corresponding health examination measures.

Setting Shiga prefecture, Japan, from April 2000 to March 2006.

Participants 3~~9~~,213~~14~~ participants aged 40 years and over.

Main outcome measures Mean ~~annual~~ medical expenditure per year.

Methods Gamma regression models were applied to examine how the number of CVD risk factors affects ~~annual~~mean medical expenditure. The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual

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blood glucose≥200 mg/dl), and smoking (current smoker). Sex- and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40 to 64) populations.

Results The mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group was only 113~~3~~0,000 Yen at age 50 (men: 11033~~,~~,708413 Yen, women: 10715,109~~470~~ Yen), but this expenditure was six to seven times higher for 80-year-olds who have three or four CVD risk factors (men: 974603,351~~449~~ Yen, women: ~~906,821~~765,673 Yen). The total overspend (excess fraction) was larger for the non-elderly (men: 15~~0~~.~~42~~%, women: 11~~9~~.13%) than for the elderly (men: -0.1~~7~~%, women: 5~~4~~.2~~7~~%) and largely driven by people with one or two CVD risk factors, except for elderly men.

Conclusion ~~AOur~~ The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors~~quantitative assessments~~ showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Keywords: Cost ~~minimization~~ analysis, Cardiovascular disease risk factor, Medical expenditure, Japan, Elderly population

Article Focus

>Cardiovascular disease risk factors are often clustered in an individual, which seriously increases the likelihood of suffering from cardiovascular disease and this clustering of risk factors also

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increases medical expenses.

> The present study examined ~~how~~ age~~-~~ and sex ~~-~~specific clustering of cardiovascular risk factors, and how it affected ~~trends influence total~~ medical expenditure ~~and assessed how the clustering of CVD risk factors affects~~in the Japanese population.

Key Messages

>The total overspends attributable to cardiovascular risk factors ~~of annual medical expenditure~~ is larger ~~for~~ among the non-elderly population ~~than for the elderly~~ in Japan.

>Larger medical overspends were driven by the groups with one or two risk factors rather than by ~~as opposed to~~ those with three or four, except for men aged 65 and over. ~~risk factors, except for elderly men.~~

Strengths and Limitations of This Study

>The statistical modelling technique which we applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper.

> The use of large comprehensive community-based database of health examination and medical expenditure brought us the stratified information by sex and age.

>Our focus on the elderly, which is considered to be a vulnerable and sometimes frail group, is especially important in developed countries where the proportion of the elderly is increasing.

>The medical expenditure was evaluated over a relatively short time period (six years) despite

investigating long-term effects, such as stroke and myocardial infarction.

Introduction

Hypertension, dyslipidemia, diabetes, and smoking are well-established risk factors for cardiovascular disease (CVD), and the damage caused by these factors is widespread across the developed world.[1] However, it is also well recognized in the literature that a combination of these risk factors in an individual increases the risk of CVD.[2] For example, several studies have shown that the clustering of metabolic risk factors more than doubles the likelihood of CVD mortality.[3,4] Moreover, from a health economics perspective, these individual CVD risk factors[5–7] and their combination[8–11] have also been reported to increase total medical expenditure in developed countries. Indeed, the public health sectors in many western nations are now facing considerable challenges because of such spiralling medical expenses.

From a financial viewpoint, the elderly population (persons aged 65 and over) is the greatest consumer of medical resources. However, even though it is clear that individual medical bills differ by age group, few studies have investigated age-specific medical expenses because of methodological issues, such as insufficient sample sizes and inappropriate statistical models. To help bridge this gap in the body of knowledge on this topic, a comprehensive community-based database for medical expenditure, which includes approximately 60,000 individuals, has been developed in

Shiga, Japan. This database consists of individuals' health examinations and their medical expenses over a three- to five-year period. Exploring this database allows us to perform an age-specific cost ~~minimization~~ analysis using Gamma regression models, especially for the elderly population. The present study ~~thus examines howconducted~~examined the age- and sex-specific proportion and distribution of medical expenditure attributable for the number of CVD risk factors ~~trends influencequantitative assessments of total medical expenditure and assessesexamines how the clustering of CVD risk factors affects~~in the Japanese population.

Methods

The medical expenditure system in Japan

The payment of medical expenses in Japan is based on a public medical insurance institution that comprises two systems. Since 1961, all Japan residents have been required to enroll in one of these two insurance systems under the so-called 'health insurance for all' scheme. First, the National Health Insurance (NHI) scheme covers self-employed workers (e.g. farmers, fishers, shopkeepers), retirees, and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (e.g. Health Insurance Society, Mutual Aid Association) covers company employees and their dependents. These two systems cover 65.3% and 34.7% of the Japanese population, respectively. All charges are strictly controlled by a service-specific fee

schedule set by the national government that is constant regardless of insurance system or health institution.

Study population and data

The comprehensive dataset used in this study comprised 64,450 NHI beneficiaries in Shiga prefecture in central Japan. Data on medical expenses and annual health examinations are both key components of this database. Medical expenses data were collected from the database of the Shiga Health Insurance Organization, which is a local branch of the NHI. The original database provides data from April 2000 to March 2006. For the economic evaluation, we ~~calculated~~used a mean ~~annual~~ medical expenditure ~~as the sum of monthly~~(per year), which was calculated by summing all medical expenditure throughout the observation periods and divided by the total ~~periods of observation.~~observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year). The data of an annual health examination were provided from every local municipality of Shiga prefecture. In Japan, an annual health examination was free of charge or inexpensive for all Japanese, which is entitled by the law (Act on Assurance of Medical Care for Elderly People). Those data were appropriately stored with security protections in every local municipality. Data on annual health examinations from April 2000, which included the baseline information for our study, were provided from all 26 local municipalities in Shiga prefecture. Both medical expenses and health examination measures were merged into the database

using individual identification information (i.e. name, sex, and date of birth) for the administrative use. This merging process was conducted by the Shiga Health Insurance Organization, the public agency for paying insurance in Shiga. The anonymous dataset were extracted from the database and then, participants who displayed signs of blood pressure, serum total cholesterol, casual blood glucose, and smoking habits (see next subsection) were included in the analysis. The participants who have not censored during whole follow-up period were included in the analysis (n=331,211139). Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Statistical analysis

Specifically, the four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (serum total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker). All participants were classified into four categories (i.e. none, one, two, and three or four) based on these four CVD risk factors. The unit of medical expenditure was set as Japanese Yen (i.e. 100 Japanese yen (JPY) = 0.81 pounds (GBP), at the exchange rates published on 10 August 2012).

~~Because data on individual medical expenses differed by the period of subscription to the NHI, individual medical expenses were divided by these periods of subscription and expressed as the~~

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~~mean expenses per year of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.~~

A gamma regression model, which is a member of generalized linear models[12], was used to estimate the mean ~~annual~~ medical expenditure of the abovementioned four categories after adjusting for confounding factors. As medical expenditure data usually involve a ~~substantial~~certain proportion of zeros and some extreme values, their distribution was skewed to the right[13–15]. A gamma regression is the best modelling approach to deal with this skewness.

Statistical models were formulated by sex and age. Specifically, we estimated age-specific ~~annual~~ medical expenditure (per year) for the following four ages: 50 years, 60 years, 70 years, and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in Shiga prefecture was considered using the generalized estimating equation (GEE) approach[12], which accounts for any correlation within each municipality.

To describe how the increasing number of CVD risk factors affects total medical expenditure in Japan, age-adjusted mean ~~annual~~ medical expenditure and the corresponding number of participants were also graphed, both for the elderly (aged 65 and over) and for the non-elderly (aged 40 to 64) populations. The cost ratios and overspend (excess fraction) were also calculated for each CVD risk factor group. The cost ratio represents the estimated ~~annual~~mean medical expenditure

of the corresponding group divided by the reference (i.e. the no CVD risk factor group), while overspend was calculated as the proportion of a certain group's excess medical expenditure relative to the whole population. This overspend can be interpreted as the medical expenditure that would not have occurred if the participants had possessed no CVD risk factors. All statistical analysis was performed using SAS release 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 compares the baseline characteristics of the four CVD risk factor groups. As the number of CVD risk factors increases, the means of systolic blood pressure, total cholesterol, and blood glucose and the proportion of current smokers grow in both men and women. The most prevalent CVD risk factors in the study participants are, first, hypertension in both men and women followed by smoking in men and cholesterol in women.

Figure 1 shows the age-specific estimated ~~annual~~mean medical expenditure (per year) for each CVD risk factor group by sex and age. Most age group graphs indicate a gradual increase in medical expenditure as the number of CVD risk factors rises for both men and women. This figure shows that the mean ~~annual~~ medical expenditure (per year) for the no CVD risk factor group is just 11~~3~~0,000 Yen at age 50 (men: 11033~~,708413~~ Yen, women: 107,109~~15,470~~ Yen), but that this expenditure is sex to seven times higher for 80-year-olds who have three or four CVD risk factors

(men: 974603,351,449 Yen, women: 906,821765,673 Yen).

Figure 2 shows the distribution of the number of CVD risk factors and their corresponding mean annual medical expenditure (per year) for the four subgroups (i.e. non-elderly men, elderly men, non-elderly women, elderly women) adjusted by age. The corresponding cost ratios and overspends (excess fractions) in each group are also shown by sex and age. The adjusted annualmean medical expenditure increases as the number of CVD risk factors rises, meaning that the cost ratio for the group with three or four CVD risk factors increases by more than 40% relative to the reference group. These trends were most obvious in non-elderly menelderly women (cost ratio: 1.7486). The total overspend was larger in the non-elderly population (men: 150.42%, women: 119.13%) than it was in the elderly (men: -0.17%, women: 54.27%). The total overspend was mostly driven by the groups with one (non-elderly men: 63.86%, non-elderly women: 74.49%, elderly women: 3.70%) or two risk factors (non-elderly men: 65.84%, non-elderly women: 34.51%, elderly women: 1.34%) compared with three or four risk factors (non-elderly men: 1.82%, non-elderly women: 0.23%, elderly women: 0.23%), with the exception of elderly men.

Discussion

We performed a community-based cost minimization analysis to investigate the sex- and age-specific effects of CVD risk factor clustering on total medical expenditure in Japan. We

measured the relative increases (cost ratios) and population impacts (overspends) and found that annual medical expenditure increases as the number of CVD risk factors rises in all age and sex groups. While the relative increase in the group with three or four CVD risk factors was greatest, the population impacts on total medical expenditure were larger among the group with one or two CVD risk factors.

The findings from the Framingham study have already shown that Medicare costs increase with combinations of risk factors, such as hypertension, smoking, and hypercholesterolemia.[8] Studies from the United States[9] and Japan[10,11] have also shown similar increasing patterns in the community setting. Our study showed that the cost ratios in the three or four CVD risk factor group were between 1.44 and 1.74, which are similar to the values found in the Framingham study[8] and another study in Japan[10]. However, other studies have found relatively larger ratios, such as 1.84–2.45 in the United States[9] and 1.91 in Japan[11], since medical expenditure is largely affected by the insurance system, study participants, and the region. The different characteristics of these previous studies, such as the definition of risk factors, length of study periods, and estimation procedures (statistical models), also affect their results.

The strength of our study is that the statistical modelling technique applied was suitable for analysing skewed medical expenditure data in contrast to a previous paper. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using

this statistical model in the cost data analysis [13]. The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome. We applied a Gamma regression model[12–15] for the cost ~~minimization~~ analysis[16] in order to investigate in-depth sex- and age-specific attributes, which is difficult in a stratified analysis. Our focus on the elderly is especially important in developed countries, where the ageing population is increasing the proportion of the elderly, which is considered to be a vulnerable and sometimes frail group.

It is important to note that individual medical expenses were highest in the three or four CVD risk factor group for all subgroups. This population would thus be the main target for high-risk approaches to contain medical expenditure growth. High-risk strategies, such as comprehensive health guidance by public health nurses, dieticians, or physicians, can be readily understood and they can strongly motivate people to change their lifestyles to manage CVD risk factors.

However, from the viewpoint of total medical expenditure, people with one or two CVD risk factors are not negligible. This population had a greater influence on total medical expenditure than did the high-CVD risk factor group, especially in the non-elderly, which accounted for more thqn 10~~9~~%– of total medical expenditure when the one and two CVD risk factor groups were combined compared with 54.04% for elderly women and ~~-~~0.0~~7~~% for elderly men. However, it is

difficult to implement effective high-risk strategies because of the large population of people with one or two CVD risk factors. For this group, a population strategy may be useful for gradually lowering the distribution of CVD risk factors[17].

The present study has several limitations. ~~First, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.~~First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the "referent" mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study. Second, medical expenditure was evaluated over a relatively short time period (six years) despite investigating long-term effects. As severe health events such as stroke and myocardial infarction can occur after a long interval in high-risk individuals, excess medical expenditure might be underestimated. Third, data on fasting blood glucose, triglycerides, and HDL-cholesterol were unavailable. ~~Finally, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable. Thus, further studies are required to clarify the effects of these~~

~~variables~~Finally, because the public medical insurance system in Japan is different from those in other developed countries, we should be cautious when comparing the absolute values of medical expenses for participants in the present study.

In conclusion, this investigation into the sex- and age-specific effects of CVD risk factors on medical expenditure in Japan showed a large relative increase in people with three or four CVD risk factors. However, the population impacts on total medical expenditure were larger among people with one or two CVD risk factors, especially in non-elderly women. A high-risk approach for people with three or four CVD risk factors and a population approach for the majority are thus both necessary to reduce total medical expenditure in Japan.

Contributors

YM was involved in database management, data analysis, data interpretation and wrote the manuscript. TO designed the study and was involved in database management, data interpretation and wrote the manuscript. KN was involved in data interpretation and writing the manuscript. KM was involved in data interpretation and writing the manuscript. UH was involved in data interpretation and writing the manuscript.

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Competing interests

None

Ethics approval

Medical research ethics committee approval was granted by the Shiga University of Health Science Research Ethics Committee (17-20-1).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Table 1. The baseline characteristics of study participants, Shiga prefectural follow-up study of medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4890; women:11,737			Men:6892, women:10,520			Men:2337, women:2362			Men:262, women:114		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	11	-	68	11	-	67	10	-	65	10	-
Systolic blood pressur	123	11	0	138	19	54	148	17	87	151	14	96
Total choresterol	187	28	0	191	31	5	201	41	23	231	41	65
Blood glucose	104	24	0	107	30	1	118	51	8	187	95	49
Current smokers	-	-	0	-	-	39	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	10	-	66	10	-
Systolic blood pressur	122	12	0	143	18	70	150	16	92	155	15	100
Total choresterol	199	25	0	214	34	23	248	33	80	260	28	91
Blood glucose	98	19	0	102	27	1	114	50	8	174	93	44
Current smokers	-	-	0	-	-	7	-	-	20	-	-	68

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men:4187; women:9924			Men:5947, women:8953			Men1945, women:1964			Men:206, women:87		
	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**	Mean	SD	%**
Men												
Age	70	10	-	68	11	-	67	10	-	65	10	-
Systolic blood pressure	124	11	0	138	19	55	148	17	87	151	15	96
Total choresterol	188	27	0	191	31	5	202	41	23	234	39	68
Blood glucose	103	23	0	106	29	1	118	50	8	178	94	45
Current smokers	-	-	0	-	-	38	-	-	82	-	-	94
Women												
Age	66	11	-	69	10	-	68	9	-	66	9	-
Systolic blood pressure	122	12	0	143	18	70	150	15	93	156	15	100
Total choresterol	200	24	0	214	34	23	249	32	82	261	23	94
Blood glucose	98	19	0	102	27	1	112	46	7	168	92	39
Current smokers	-	-	0	-	-	6	-	-	18	-	-	70

* The four CVD risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg), hypercholesterolemia (total cholesterol≥240 mg/dl), high blood glucose (casual blood glucose≥200 mg/dl), and smoking (current smoker).

** For each CVD risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

Figure legends

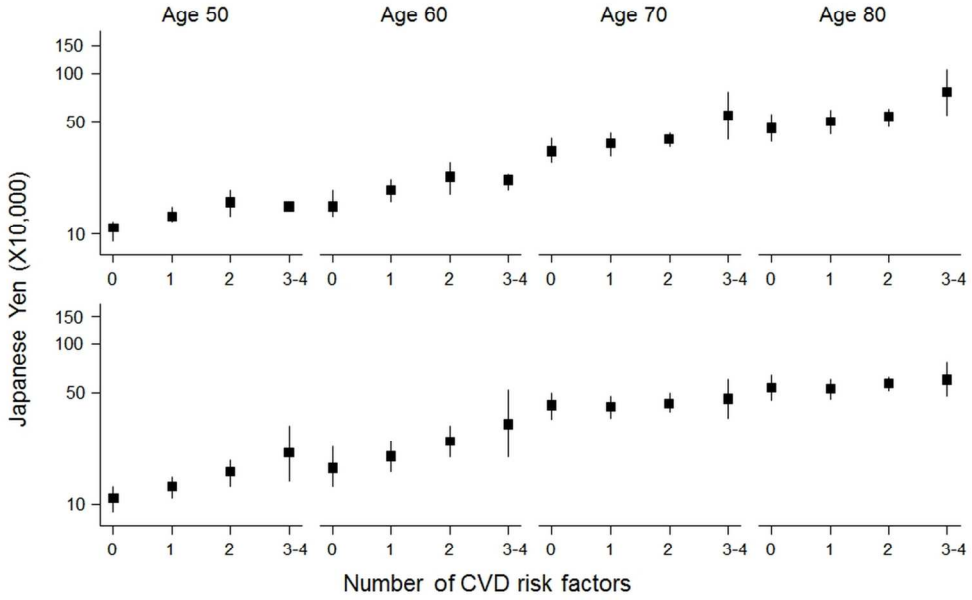
Figure 1. The age- and sex-specific estimated ~~annual~~mean medical expenditure (per year) by CVD risk factor group.

The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the ~~annual~~mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% confidence intervals.

Figure 2. The distribution of the number of CVD risk factors, their estimated mean ~~annual~~ medical expenditure~~,~~ (per year), and overspend in the population: (A) men aged 40 to 64, (B) men aged 65 and over, (C) women aged 40 to 64, and (D) women aged 65 and over.

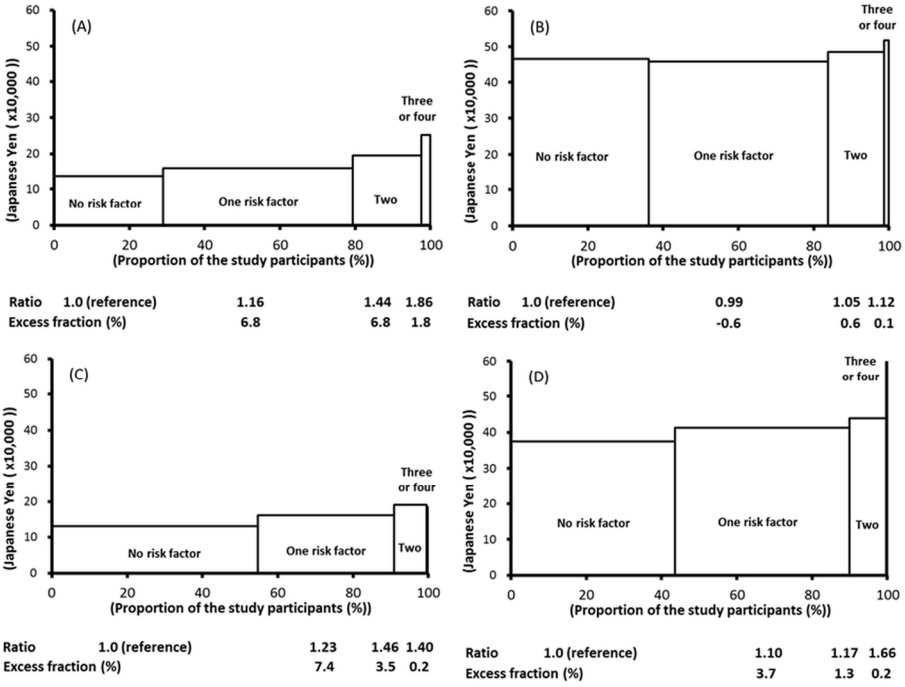
The Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (i.e. the no CVD risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

Fig. 1



120x90mm (300 x 300 DPI)

Fig 2



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