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１）宮崎純子、伯井朋子、本田瑛子、松本裕子、梅沢光政、羽山実奈、梶浦貢、岡田武夫、木山昌彦、中村正和、磯博康、北村明彦．地域住民の血圧上昇に関わる食事因子の検討．第72回日本公衆衛生学会（津）

２）伯井朋子、宮崎純子、本田瑛子、松本裕子、羽山実奈、梶浦貢、岡田武夫、木山昌彦、中村正和、北村明彦．動脈硬化進行に関する危険因子、食事因子の検討．第72回日本公衆衛生学会（津）

３）梅澤光政、長尾匡則．日本人における体重変化と食行動の関連（CIRCS）．第41回獨協医学会（壬生）

H.知的財産権の出願・登録状況

なし

〔研究協力者〕

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表1 食習慣に関する質問項目

(質問紙の記載)	(本文・表中の表記)
・朝食を抜くことがよくありますか	・朝食を食べない
・夕食後1～2時間以内に床につきますか	・夕食後、1～2時間で寝る
・ついついお腹いっぱい食べるほうですか	・つい満腹まで食べる
・間食または夜食をほぼ毎日とりますか	・間食夜食を毎日摂っている
・砂糖入りの飲料(コーヒー、ジュース、炭酸飲料)をほぼ毎日飲みますか	・砂糖入り飲料を毎日摂っている
・油料理(天ぷら、フライ、炒め物など)をほぼ毎日食べますか	・油料理を毎日摂っている
・卵をほぼ毎日食べますか	-
・脂身の多い肉類(バラ肉、ひき肉、ロース肉、加工肉)を食べる日は、週に3日以上ですか	-
・魚介類を食べる日は、週に3日以上ですか	-
・煮物などの味付けは、濃いほうですか	-
・汁物(みそ汁、スープ)を1日2杯以上飲みますか	-
・麺類の汁をほとんど全部飲みますか	-
・塩蔵品(塩ざけ、たらこ、佃煮など)を食べる日は、週に3日以上ですか	-
・漬物や味付けしているおかずに、しょう油やソースをかけることが多いですか	-
・漬物を1日2回以上食べますか	-
・漬物以外の野菜・海草・きのこ類をほぼ毎食食べますか	・野菜や海藻を毎食摂っている
・果物をほぼ毎日食べますか	・果物を毎日摂っている
・大豆製品(豆腐、油揚げ、納豆、煮豆など)をほぼ毎日食べますか	-
・乳製品(牛乳、ヨーグルトなど)をほぼ毎日とりますか	-

表2 対象者の属性-各食習慣への回答状況による比較ー

	質問への回答(初回健診時/最終健診時)					
	はい/はい (Group 1)	はい/いいえ (Group 2)	いいえ/はい (Group 3)	いいえ/いいえ (Group 4)	欠損	P for difference
<朝食を食べない>						
人数	1603	1168	588	11119	11	
年齢(歳)	41.9	44.2**	45.3**	50.2**	60.9**	-
性別(%男性)	76	74	65	57	82	<0.01
Body mass index (kg/m^2)[a]	23.2	23.6**	23.6**	23.2	23.8	-
現在飲酒者 (%)	68	66	61	54	36	<0.01
現在喫煙者 (%)	60	47	43	26	55	<0.01
運動習慣がある者(%)	30	36	36	43	20	<0.01
<夕食後、1～2時間で寝る>						
人数	2949	1357	1697	8465	21	
年齢(歳)	47.8	47.6	48.4	49.1**	58.7**	-
性別(%男性)	83	74	68	50	62	<0.01
Body mass index (kg/m^2)[a]	23.4	23.5	23.3	23.1**	23.2	-
現在飲酒者 (%)	73	65	62	49	48	<0.01
現在喫煙者 (%)	43	36	37	27	29	<0.01
運動習慣がある者(%)	37	39	40	43	45	<0.01
<つい満腹まで食べる>						
人数	6507	1966	1349	4638	29	
年齢(歳)	45.8	48.3**	49.4**	52.4**	61.3**	-
性別(%男性)	60	63	61	62	59	0.28
Body mass index (kg/m^2)[a]	24.0	23.8*	22.7**	22.1**	23.5	-
現在飲酒者 (%)	58	59	56	56	48	0.02
現在喫煙者 (%)	32	33	33	33	24	0.22
運動習慣がある者(%)	39	41	40	43	32	<0.01
<間食夜食を毎日摂っている>						
人数	2295	1484	1437	9248	25	
年齢(歳)	47.3	49.0**	48.9**	48.8**	60.7**	-
性別(%男性)	33	47	49	72	48	<0.01
Body mass index (kg/m^2)[a]	23.3	23.8**	23.1	23.2	23.3	-
現在飲酒者 (%)	35	43	46	67	52	<0.01
現在喫煙者 (%)	17	26	27	38	20	<0.01
運動習慣がある者(%)	38	36	38	42	42	<0.01
<砂糖入り飲料を毎日摂っている>						
人数	3903	2051	1117	7400	18	
年齢(歳)	47.4	47.5	50.2**	49.3**	62.9**	-
性別(%男性)	70	68	60	55	56	<0.01
Body mass index (kg/m^2)[a]	22.7	23.6**	23.3**	23.4**	24.2	-
現在飲酒者 (%)	55	61	55	57	28	<0.01
現在喫煙者 (%)	47	38	30	24	39	<0.01
運動習慣がある者(%)	34	37	38	46	18	<0.01
<油料理を毎日摂っている>						
人数	1820	1649	1359	9644	17	
年齢(歳)	42.5	46.2**	45.8**	50.5**	62.5**	-
性別(%男性)	70	67	68	57	71	<0.01
Body mass index (kg/m^2)[a]	23.6	23.6	23.3	23.1**	23.3	-
現在飲酒者 (%)	63	61	60	55	47	<0.01
現在喫煙者 (%)	38	37	33	31	35	<0.01
運動習慣がある者(%)	37	38	37	42	13	<0.01
<野菜や海藻を毎食摂っている>						
人数	4040	1735	2678	6015	21	
年齢(歳)	53.2	47.9**	50.2**	45.0**	58.9*	-
性別(%男性)	50	66	54	70	67	<0.01
Body mass index (kg/m^2)[a]	23.3	23.3	23.4	23.1**	23.7	-
現在飲酒者 (%)	50	60	54	62	52	<0.01
現在喫煙者 (%)	23	33	30	40	24	<0.01
運動習慣がある者(%)	47	45	40	36	25	<0.01
<果物を毎日摂っている>						
人数	3611	1459	1611	7790	18	
年齢(歳)	54.9	50.3**	49.8**	45.1**	62.1**	-
性別(%男性)	48	52	60	69	78	<0.01
Body mass index (kg/m^2)[a]	23.1	23.5**	23.1	23.3*	23.4	-
現在飲酒者 (%)	47	49	58	64	56	<0.01
現在喫煙者 (%)	16	24	29	42	33	<0.01
運動習慣がある者(%)	51	42	42	36	41	<0.01

[a]: 性年齢調整値

*: P<0.05、**: P<0.01 (Group 1との比較)

表3 各食習慣への回答状況別にみたBMI変化量

	BMI変化量	質問への回答(初回健診時/最終健診時) はい/はい (Group 1)	はい/いいえ (Group 2)	P for difference	いいえ/はい (Group 3)	P for difference	いいえ/いいえ (Group 4)	P for difference	P for ANCOVA
朝食を食べない	人数	1603	1168		588		11119		
	性年齢調整値	0.16	0.13	0.50	0.02	0.02	0.00	<0.01	<0.01
	多変量調整値[a]	0.09	0.14	0.29	0.01	0.23	0.01	0.03	<0.01
夕食後、1～2時間で寝る	人数	2949	1357		1697		8465		
	性年齢調整値	0.00	0.01	0.89	0.08	0.04	0.03	0.39	0.21
	多変量調整値[a]	−0.03	0.04	0.14	0.07	0.02	0.03	0.05	0.09
つい満腹まで食べる	人数	6507	1966		1349		4638		
	性年齢調整値	0.06	−0.40	<0.01	0.47	<0.01	0.03	0.24	<0.01
	多変量調整値[a]	0.11	−0.35	<0.01	0.42	<0.01	−0.05	<0.01	<0.01
間食夜食を毎日摂っている	人数	2295	1484		1437		9248		
	性年齢調整値	0.05	−0.14	<0.01	0.12	0.11	0.03	0.48	<0.01
	多変量調整値[a]	0.03	−0.10	<0.01	0.07	0.34	0.04	0.89	<0.01
砂糖入り飲料を毎日摂っている	人数	3903	2051		1117		7400		
	性年齢調整値	0.16	0.04	<0.01	0.00	<0.01	−0.05	<0.01	<0.01
	多変量調整値[a]	0.10	0.06	0.30	0.00	0.02	−0.02	<0.01	<0.01
油料理を毎日摂っている	人数	1820	1649		1359		9644		
	性年齢調整値	0.08	−0.07	<0.01	0.21	<0.01	0.00	0.03	<0.01
	多変量調整値[a]	0.06	−0.05	0.01	0.19	<0.01	0.01	0.10	<0.01
野菜や海藻を毎食摂っている	人数	4040	1735		2678		6015		
	性年齢調整値	−0.04	0.05	0.02	−0.03	0.91	0.09	<0.01	<0.01
	多変量調整値[a]	0.00	0.06	0.08	−0.01	0.70	0.05	0.07	0.07
果物を毎日摂っている	人数	3611	1459		1611		7790		
	性年齢調整値	−0.04	−0.03	0.85	0.00	0.26	0.07	<0.01	<0.01
	多変量調整値[a]	−0.01	0.00	0.78	0.02	0.45	0.05	0.04	0.17

[a]調整因子：年齢、性別、ベースライン時BMI(kg/m^2)、飲酒の有無、喫煙の有無、運動習慣の有無、他の食習慣
P for difference：Group 1との比較

Saito I, Yamagishi K, Chei CL, Cui R, Ohira T, Kitamura A, Kiyama M, Imano H, Okada T, Kato T, Hitsumoto S, Ishikawa Y, Tanigawa T, Iso H. Total and high molecular weight adiponectin levels and risk of cardiovascular disease in individuals with high blood glucose levels. Atherosclerosis. 2013;229:222-7.

日本人高血糖者における血中アディポネクチン濃度と循環器疾患発症リスク

＜目的＞
血中アディポネクチン濃度と循環器疾患の関連は年齢や健康状態によって様々であると報告されている。その中で、高血糖者における血中アディポネクチン濃度と循環器疾患の発症リスクの関連も明らかではない。そこで、本研究では高血糖者における血中アディポネクチン濃度と循環器疾患発症リスクの関連を検討した。

＜方法＞
Nested case-control study の手法を用いた。対象者は、CIRCS 研究グループに含まれる日本国内 3 地域の一般住民男女および大洲 Study に参加している一般住民男女で、一定の期間内（CIRCS 研究が 1984 年から 1992 年、大洲 Study が 1996 年から 1998 年）に健診を受診し、血清を冷凍保存している 40-85 歳の 15,566 人とした。この中で、循環器疾患の発症例 117 件と性、年齢、受診年、地域、採血状況（空腹 or 非空腹）、血糖値をマッチさせた対症例を 1 対 2 の割合でとり、分析を行った。対象者を血中総アディポネクチン濃度及び血中 HMW（high-molecular weight）アディポネクチン濃度に従って 4 分位で分け、それぞれの血中濃度が最も低かった群に対する、他の群の循環器疾患発症リスクを算出した。また、HMW アディポネクチン濃度/総アディポネクチン濃度比（HMW/Total 比）を算出し、比の値の 4 分位で分け、比が最も小さかった群に対する他の群の循環器疾患発症リスクも算出した。
＜結果＞
平均 12.3 年の追跡を行った。全対象者における分析では、血中総アディポネクチン濃度及び血中 HMW アディポネクチン濃度、HMW/Total 比は循環器疾患の発症リスクと関連を認めなかった。対象者を受診時の年齢で層別したところ、40-69 歳の群では血中 HMW アディポネクチン濃度及び HMW/Total 比が循環器疾患発症リスクと負の関連を示した。血中総アディポネクチン濃度は循環器疾患の発症リスクと関連を認めなかった。70-85 歳の群ではいずれの指標も循環器疾患の発症リスクと関連を認めなかった。

＜結論＞
日本人の 69 歳以下の男女において、血中 HMW アディポネクチン濃度及び HMW/Total 比が循環器疾患発症リスクと負の関連を示した。

Shimizu Y, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, Ishikawa Y, Shimamoto T, Yamagishi K, Tanigawa T, Iso H; CIRCS Investigators. Adult Height and Body Mass Index in Relation to Risk of Total Stroke and its Subtypes: The Circulatory Risk in Communities Study. J Stroke Cerebrovasc Dis. 2013;S1052-3057:00230-9.

日本人の身長及び Body Mass Index と脳卒中発症リスク：the Circulatory Risk in Communities Study(CIRCS)

＜目的＞

身長が脳卒中の発症リスクと関係することが報告されている。これは身長が小児期におかれた環境を反映する指標と考えられているためである。しかしながら、身長に加えて、現在の体格も含めて脳卒中の発症リスクとの関連を調べた研究は少ない。そこで、本研究では脳卒中の発症リスクについて、身長及び Body Mass Index(BMI)の関連を検討した。

＜方法＞

Prospective cohort study の手法を用いた。対象者は、CIRCS 研究グループに含まれる日本国内 4 地域の一般住民男女で、一定の期間内（2 つの地域が 1985 年から 1990 年、1 つの地域が 1985 年から 1991 年、残る一つが 1985 年から 1994 年）に健診を受診した 40-69 歳の 12,222 人である。対象者を性別に身長で 4 分位に分け、身長が最も低い群に対する他の群の脳卒中発症リスクを、Cox 比例ハザードモデルを用いて算出した。

＜結果＞17 年間の追跡の間に 565 人が脳卒中を発症した（脳梗塞 326 人、出血性脳卒中 186 人）。身長は男女ともに全脳卒中の発症リスクと負の関連を示した。特に BMI が 23kg/m^2 未満の者ではその傾向が顕著であった。一方、BMI が 23kg/m^2 以上の者では、身長と全脳卒中の発症リスクとの間に有意な関連は認められなかった。BMI が 23kg/m^2 未満の者について病型別に身長との関連を分析したが、男女ともに身長は脳梗塞、出血性脳卒中のいずれとも有意な負の関連を示した。

＜結論＞

日本人の男女において、身長と脳卒中の発症リスクに負の関連が認められた。また、その傾向は BMI23 kg/m^2 未満の者で顕著であった。

Ⅳ．研究成果の刊行物・別刷
（一覧は各個別研究の末尾に記載）

BMJ open

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 mm Hg or diastolic blood pressure ≥90 mm Hg), hypercholesterolaemia (serum total cholesterol ≥240 mg/dl), high blood glucose (casual blood glucose ≥200 mg/dl) and smoking (current smoker). Sex-specific and age-specific investigations were carried out on the elderly (aged 65 and over) and non-elderly (aged 40–64) 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 6–7 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 that 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.

Conclusions: 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.

ARTICLE SUMMARY

Article focus

- Cardiovascular disease (CVD) risk factors are often clustered in an individual which seriously increases the likelihood of suffering from CVD and this clustering of risk factors also increases medical expenses.
- The present study examined age-specific 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 (6 years) despite investigating long-term effects, such as stroke and myocardial infarction.

INTRODUCTION

Hypertension, dyslipidaemia, 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-recognised 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 combinations[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 3-year to 5-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-specific and sex-specific proportion and distribution of medical expenditure attributable to the number of CVD risk factors in the Japanese population.

METHODS

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 Japanese residents have been required to enrol 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 (eg, farmers, fishermen and shopkeepers), retirees and their dependents. The elderly in Japan are thus most often covered by the NHI scheme. The other insurance system (eg, Health Insurance Society and 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-up all medical expenditure throughout the observation periods and dividing it by the total observation periods of the number of months. This monthly measure is multiplied by 12 to transform a mean medical expenditure (per year). The data of an annual health examination were provided by every local municipality of Shiga prefecture. In Japan, an annual health examination is free of charge or is inexpensive for all Japanese, entitled by the law (Act on Assurance of Medical Care for Elderly People). These 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 from all 26 local municipalities in the Shiga prefecture. Both medical expenses and health examination measures were merged into the database using individual identification information (ie, 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 had not been censored during the entire 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 mm Hg or diastolic blood pressure ≥90 mm Hg), hypercholesterolaemia (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 (ie, none, one, two and three or four) based on the four CVD risk factors. The unit of medical expenditure was set as Japanese yen (ie, 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 generalised linear models,[12] was used to estimate the mean medical expenditure of the a forementioned 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] 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, 60, 70 and 80 years. These estimated expenses were then plotted against the number of CVD risk factors. The regional variation of local municipalities in the Shiga prefecture was considered using the generalised estimating equation 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 40–64) 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 (ie, 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 no CVD risk factors. All statistical analyses were performed using SAS release 9.20 (SAS Institute Inc, Cary, North Carolina, 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 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 6–7 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 (ie, non-elderly men, elderly men, non-elderly women and 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

Table 1 Baseline characteristics of study participants, Shiga prefectural follow-up study on health examination and medical expenditure, 2000–2006

	Number of cardiovascular risk factors*											
	0			1			2			3 or 4		
	Men: 4187; women: 9924			Men: 5947; women: 8953			Men: 1945; women: 1964			Men: 206; women: 87		
	Mean	SD	Percentage†	Mean	SD	Percentage†	Mean	SD	Percentage†	Mean	SD	Percentage†
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 cholesterol	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 cholesterol	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 cardiovascular disease risk factors analysed in this study were defined as follows: hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), hypercholesterolaemia (total cholesterol ≥240 mg/dl), high blood glucose (casual blood glucose ≥200 mg/dl) and smoking (current smoker).
†For each cardiovascular disease risk factor, the proportions (%) of participants who possess this risk factor are shown in each category.

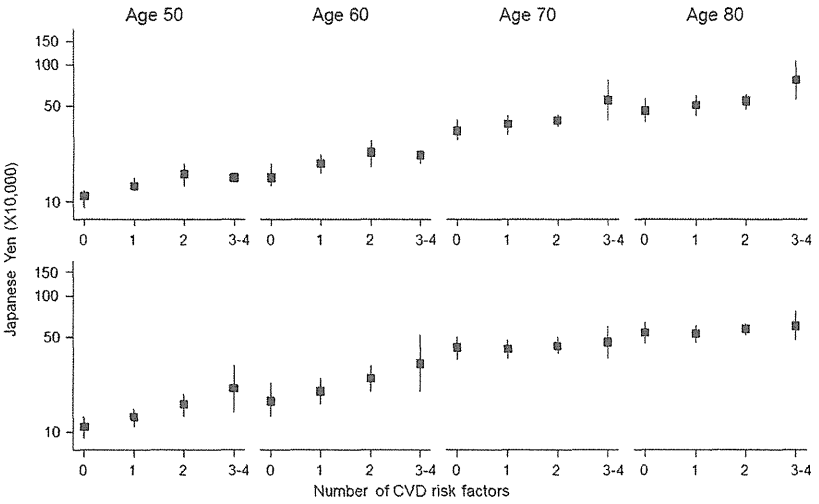

Figure 1 The age-specific and sex-specific estimated mean medical expenditure (per year) by cardiovascular disease (CVD) risk factor group. The Gamma regression was used to estimate the mean medical expenditure in the model. The black rectangles show the mean medical expenditure (per year) of each CVD risk factor group and the corresponding solid lines show their 95% CI.

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

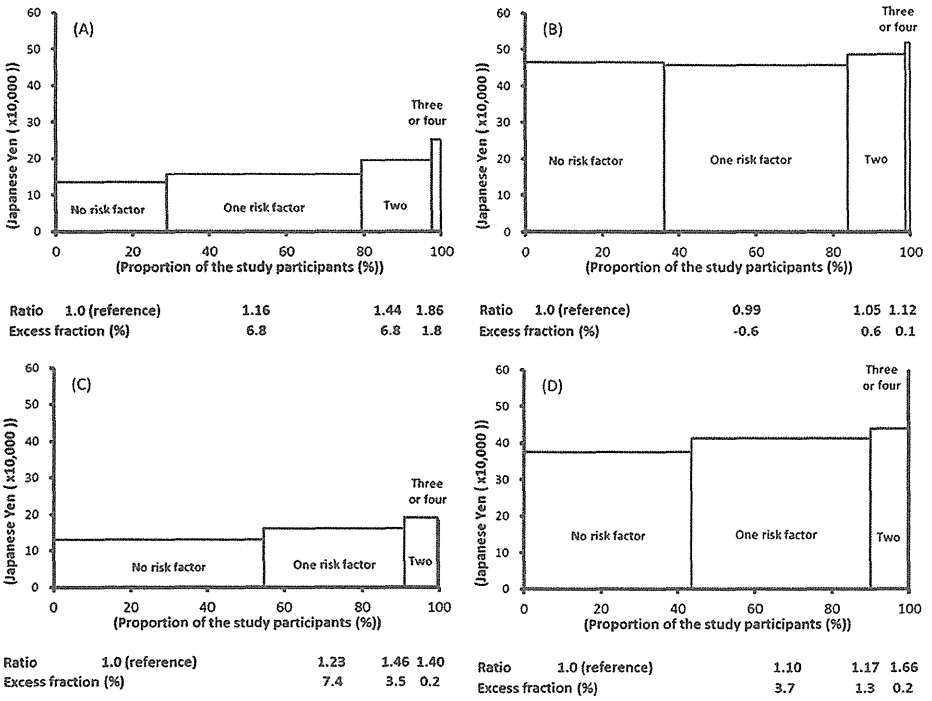

Figure 2 The distribution of the number of cardiovascular disease risk factors, their estimated mean medical expenditure (per year) and overspending by the population: (A) men aged 40–64, (B) men aged 65 and over, (C) women aged 40–64 and (D) women aged 65 and over. Gamma regression was used to estimate the mean medical expenditure in the model. The overspend is the difference between the expenditure of each category and the reference (ie, the no cardiovascular disease risk factor group). This was defined as the proportion of excess expenditure relative to total medical expenditure.

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 hypercholesterolaemia.[8] Studies from the USA[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 groups 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 USA[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 the 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] to investigate in-depth sex-specific 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 groups 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 than 10% of total medical expenditure when the one or 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 (eg, prescriptions), clinical conditions such as CVD history and cause of death were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of the 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 (6 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 high-density lipoprotein 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-specific 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.

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Contributors YM, TO and KN conceived the idea of the study and were responsible for the design of the study. YM was responsible for undertaking the data analysis and produced the tables and graphs. YM, TO, KN, KM and HU provided their inputs for the data analysis. The initial draft of the manuscript was prepared by YM and TO and then circulated among all authors for critical revisions. TO and YM were responsible for the acquisition of the data and YM, TO, KN, KM and HU contributed to the interpretation of the results. All authors read and approved the final manuscript.

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Competing interests None.

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ORIGINAL ARTICLE
Heart Failure

Association Between Weight Change Since 20 Years of Age With Mortality From Myocardial Infarction and Chronic Heart Failure in the Japan Collaborative Cohort (JACC) Study

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Background: Weight gain is an important risk factor of coronary artery disease, but there is limited evidence for an effect of weight change on heart failure (HF) mortality.

Methods and Results: A total of 61,571 subjects aged 40–79 years were selected. Participants were already enrolled in the Japan Collaborative Cohort (JACC) study, for whom data regarding weight at the age of 20 years of age were available. The underlying causes of death were determined based on the International Classification of Diseases. During the median 19.3-year follow-up of the cohort, there were 640 deaths from myocardial infarction (MI) and 605 deaths from HF. Men and women who had gained weight had a higher risk of mortality from MI, whereas those who had lost weight had a higher risk of mortality from HF. Compared to subjects with no weight change (within ±5.0 kg), the multivariate hazard ratios (HR; 95% confidence interval [CI]) of MI for weight change of +10.0 kg or more were 1.51 (1.11–2.06) for men and 1.80 (1.23–2.64) for women, whereas HRs of HF were 0.76 (0.51–1.13) and 0.94 (0.66–1.33), respectively. The corresponding HRs of MI for weight change of −10.0 kg or more were 0.86 (0.57–1.31) for men and 0.90 (0.54–1.53) for women, whereas those of HF were 1.33 (0.93–1.89) and 1.48 (1.04–2.12), respectively.

Conclusions: High BMI and weight gain are associated with increased risk of mortality from MI, whereas low BMI and weight loss are associated with increased risk of mortality from HF. (*Circ J* 2014; **78:** 649–655)

Key Words: Follow-up study; Heart failure; Myocardial infarction; Weight change

It is well known that obesity and weight gain are important risk factors for myocardial infarction (MI).[1–6] More than 80% of the estimated deaths attributable to obesity occur among individuals with a body mass index (BMI) >30 kg/m^2.[3] The incidence of ischemic heart disease has increased twofold in Japan during the last 20 years.[7] Furthermore, the prevalence of heart failure (HF) related to ischemic heart disease has increased in Asian populations from 1993 to 2010.[8] A recent population-based study in Western Australia reported that 78.1% of HF cases and 21.2% of deaths due to HF occurred after first acute MI.[9]

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Several prospective studies of general populations showed that obesity is a risk factor for incident HF,[10,11] while prospective studies of HF patients showed that low BMI is a risk factor of HF mortality.[12–14] A meta-analysis of 28,209 men and women experiencing HF showed that obesity was inversely associated with mortality from cardiovascular disease.[15] Interestingly, another patient-based prospective study reported that weight gain after MI was not associated with increased risk of mortality from MI.[16] These findings suggest that ideal weight management policies for primary and secondary prevention may be different. There was a U-shaped relationship between BMI and mortality from cardiovascular disease.[1,2]

To date, no population-based prospective study has examined the associations between low BMI and weight loss with the risk

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Table 1. Age-Adjusted Baseline Risk Factors vs. BMI at Baseline

	BMI at baseline (kg/m²)						P for trend
	<19.0	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥27.0	
Men	1,934	5,339	7,414	7,414	6,333	1,698	
Age (years)	61.8***	58.0***	56.9***	55.5	54.8**	54.6***	<0.001
BMI at baseline (kg/m²)	17.9***	20.1***	22.0***	23.9	25.9***	28.7***	<0.001
BMI at age the of 20 (kg/m²)	20.1***	21.3***	22.0***	22.5	22.9***	24.0***	<0.001
Alcohol consumption (g/day)	32.2*	33.8	34.1	33.7	34.2	34.7	0.03
Current smokers	66.2***	61.8***	56.1***	49.8	47.0*	45.3**	<0.001
High perceived mental stress	27.6***	22.6	20.8*	22.5	22.2	23.8	0.23
Walking ≥30 min/day	70.3	72.5***	71.1**	68.6	66.0*	62.3***	<0.001
Exercise ≥5 h/week	8.0	7.4	7.6	7.0	7.3	6.6	0.21
College or higher education	16.1***	16.4***	17.9	19.0	20.2	16.7*	<0.001
Fresh fish intake (times/week)	6.6***	6.7***	6.9	7.0	6.9	6.9	<0.001
Women	3,057	6,548	9,662	8,293	4,783	3,438	
Age (years)	59.0***	56.0	55.7	55.9	56.7***	56.8***	<0.001
BMI at baseline (kg/m²)	17.8***	20.1***	22.0***	23.9	25.9***	29.0***	<0.001
BMI at the age of 20 (kg/m²)	20.0***	21.2***	21.8***	22.2	22.5***	23.3***	0.03
Alcohol consumption (g/day)	11.1	9.6	9.4	10.2	9.6	13.1***	0.01
Current smokers	7.2***	5.6***	4.5	4.4	4.5	6.1***	0.02
High perceived mental stress	22.6***	21.5***	19.9	19.6	18.8	19.1	<0.001
Walking ≥30 min/day	71.7	73.8***	73.0***	71.2	70.9	69.2*	<0.001
Exercise ≥5 h/week	4.0	4.9	4.6	4.6	4.4	3.4**	0.19
College or higher education	12.9***	11.5***	11.6***	9.2	9.2	7.5***	<0.001
Fresh fish intake (times/week)	6.8***	6.9***	7.1	7.2	7.2	7.1	0.28

Data given as mean or %. *P<0.05; **P<0.01; ***P<0.001 compared to BMI=23.0–24.9 kg/m².
BMI, body mass index.

of mortality from HF. The present a priori hypothesis is that subjects with a high BMI or who have gained weight have an increased risk of mortality from MI, whereas those with low BMI or who have lost weight have an increased risk of mortality from HF. We therefore investigated the association between obesity and weight change with mortality due to both MI and HF among lean Japanese subjects in the Japan Collaborative Cohort (JACC) study.

Methods

Subjects

The JACC study for the evaluation of cancer risk, which was sponsored by the Ministry of Education, Sports, and Science, was conducted between 1988 and 1990. A total of 46,397 men and 64,190 women aged 40–79 years from 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires about their current height and weight, weight at 20 years of age, lifestyle and medical history.[17] Among these subjects, weight data at 20 years of age were available for 31,312 men and 42,131 women. We excluded 5,522 men and 6,350 women who had a self-reported history of lung disease, kidney disease, liver disease, HF, stroke, coronary artery disease (CAD) or cancer at baseline. Therefore, 25,790 men and 35,781 women were enrolled in the present study.

Exposure Assessment and Mortality Surveillance

BMI was calculated by dividing the weight (kg) by the height (m²). BMI at 20 years of age was estimated using reported weight at 20 years of age and current height under the assumption that height had not changed materially since 20 years of age.

Follow-up surveys were conducted annually to verify participant status. To conduct mortality surveillance in each community, investigators instigated a systematic review of the death certificates, all of which were forwarded to the public health center in the appropriate areas of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of death was coded according to the International Classification of Diseases, 10th Revision, for the National Vital Statistics, from MI (ICD I21) and from HF (I50).

The registration of death is required by the Family Registration Law and is believed to be strictly observed across Japan. Therefore, all deaths that occurred in the cohort were verified by the issuing of death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case when he or she moved. In most areas, follow-up was conducted until the end of 2009 (4 and 4 communities at the end of 1999 and 2003). The median follow-up period for all participants was 19.2 years. The Ethics Committee of the Nagoya University School of Medicine and Osaka University of School Medicine approved the study protocol.

Statistical Analysis

Statistical analysis was based on sex-specific mortality rates from MI and HF during the follow-up period, 1988 to 2009. The person-years of follow-up were calculated from the date of completion of the baseline questionnaire to the date of death, or moving out of the community, or the end of 2009, whichever occurred first. The sex-specific hazard ratios (HR) of mortality from MI and HF were defined as the death rate according to BMI at baseline categories (<19.0, 19.0–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9 and ≥27.0 kg/m²), and weight change (kg)

Table 2. Age-Adjusted Baseline Risk Factors vs. Weight Change Since 20 Years of Age

	Weight change since 20 years of age (kg)					P for trend
	−10.0 or more	−5.0 to −9.9	−4.9 to +4.9	+5.0 to +9.9	+10.0 or more	
Men	1,954	3,979	10,378	4,750	4,729	
Age (years)	64.9***	61.9***	56.1	53.7***	53.4***	<0.001
BMI at baseline (kg/m²)	20.4***	21.0***	21.9	23.7***	25.7***	<0.001
BMI at the age of 20 (kg/m²)	25.7***	23.4***	22.0	21.3***	20.5***	<0.001
Alcohol consumption (g/day)	37.3***	35.4**	33.7	32.5*	33.4	<0.001
Current smokers	71.2***	65.2***	56.0	46.8***	44.3***	<0.001
High perceived mental stress	22.7	22.2	21.0	22.8*	25.4***	<0.001
Walking ≥30 min/day	72.2	72.1	72.5	66.7***	62.9***	<0.001
Exercise ≥5 h/week	8.6*	8.3*	7.2	7.1	6.8	0.03
College or higher education	13.7**	14.1**	16.6	21.6***	21.8***	<0.001
Fresh fish intake (times/week)	7.0	7.0	6.8	6.8	6.7	0.54
Women	1,884	4,996	14,211	7,801	6,889	
Age (years)	64.1***	60.1***	55.4	54.7***	55.1*	<0.001
BMI at baseline (kg/m²)	19.9***	20.8***	22.0	23.8***	26.3***	<0.001
BMI at the age of 20 (kg/m²)	25.9***	23.7***	22.0	20.9***	20.2***	<0.001
Alcohol consumption (g/day)	10.7	10.5*	9.2	10.0	11.7***	0.008
Current smokers	8.6***	6.5***	4.3	4.5	5.4***	0.001
High perceived mental stress	24.4***	21.2***	19.4	19.4	20.5	0.09
Walking ≥30 min/day	73.4	72.8	73.8	70.9***	68.4***	<0.001
Exercise ≥5 h/week	4.4	5.1	4.6	4.2	4.0*	0.03
College or higher education	10.0	10.1	11.1	10.5	9.5***	0.16
Fresh fish intake (times/week)	6.7***	6.9*	7.1	7.2	7.1	0.84

Data given as mean or %. *P<0.05; **P<0.01; ***P<0.001 compared to weight change within 5.0 kg.
Abbreviation as in Table 1.

categories (−10.0 or more, −5.0 to −9.9, −4.9 to +4.9, +5.0 to +9.9, and +10.0 or more) from the age of 20 years onwards. BMI range of 23.0–24.9 kg/m² or a weight change within ±5.0 kg since 20 years of age was used as a reference.

The sex-specific, age-adjusted baseline characteristics of cardiovascular risk factors are presented according to weight change category, and analysis of covariance or chi-squared test were used. Age- and multivariate-adjusted tests for a linear trend across categories of BMI and weight change were conducted using linear or logistic regression models. The multivariate-adjusted HRs and their 95% confidence intervals [CIs] were calculated after adjusting for potential confounding factors using the Cox proportional hazards model.

The confounding variables at baseline included age (years), smoking status (never, ex-smoker, current smoker, consuming either 1–19 or ≥20 cigarettes/day), alcohol consumption (never, ex-drinker, current ethanol consumption 1–22, 23–45, 46–68 and ≥69 g/day), hours of exercise (almost never, or exercise of 1–2, 3–4, or ≥5 h/week), hours of walking (seldom, or walking for 1–30, 30–59, or ≥60 min/day), perceived mental stress (low, moderate and high), educational level (primary school, junior high school, high school, college, or higher than college), fresh fish intake (almost never, 1–2 times/month, 1–2 times/week, 3–4 times/week, and almost every day), and BMI at the age of 20. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

There were no apparent differences in age-adjusted means or proportions of major cardiovascular risk factors between the subjects with and without weight data at 20 years of age. The respective mean ages were 57.2 years and 56.9 years for men, and 58.5 years and 56.5 years for women. The age-adjusted mean BMI were 22.6 kg/m² and 22.7 kg/m² for men, and 22.8 kg/m² and 23.0 kg/m² for women. The age-adjusted proportions of hypertension were 20.1% and 20.2% for men, and 22.3% and 22.1% for women; those of diabetes were 6.7% and 6.7% for men, and 4.1% and 3.8% for women; those of current smokers were 54.4% and 54.0% for men, and 6.1% and 5.1% for women.

During the median 19.3-year follow-up of 25,790 men and 35,781 women aged 40–79 years, 400 men and 240 women died from MI and 301 men and 304 women died from HF. The mean age (range at baseline) of subjects who died from MI was 63.1 years (range, 40–79 years) for men, 67.0 years (range, 41–79 years) for women and 64.6 years (range, 40–79 years) for the total subjects. The respective mean ages at the endpoint were 75.2 years (range, 46–95 years), 79.1 years (range, 43–95 years) and 76.7 years (range, 43–95 years). The respective mean ages at baseline for HF were 66.9 years (range, 40–79 years), 68.3 years (range, 40–79 years) and 67.7 years (range, 40–79 years), and those at the endpoint were 77.8 years (range, 49–98 years), 81.6 years (range, 46–100 years) and 79.7 years (range, 46–100 years). The mean follow-up period in subjects who died from MI was 11.6 years for men, 11.7 years for women and 11.7 years for total subjects. The respective mean follow-up period for HF was 10.4 years, 12.8 years and 11.7 years. Mean duration between age 20 and age at baseline in subjects who died from MI was 43.1 years for men, 47.0 years for women and 44.6 years for total subjects. The respective mean duration for HF was 46.9 years, 48.3 years and 47.6 years.

Tables 1,2 list the sex-specific, age-adjusted baseline characteristics of the enrolled subjects according to the selected cat-

Table 3. Mortality From CAD and HF vs. BMI at Baseline

	BMI at baseline (kg/m²)						P for trend
	<19.0	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥27.0	
Men							
Person-year	26,924	83,691	120,055	105,207	50,917	28,425	
Myocardial infarction	36	83	100	88	50	43	
Age-adjusted HR (95% CI)	1.10 (0.74–1.63)	1.01 (0.75–1.36)	0.91 (0.68–1.21)	1.00	1.25 (0.88–1.76)	1.98 (1.37–2.85)***	0.003
Multivariate HR (95% CI)	1.12 (0.76–1.63)	0.86 (0.62–1.19)	0.94 (0.70–1.27)	1.00	1.16 (0.80–1.69)	2.06 (1.40–3.02)***	<0.001
Heart failure, n	43	74	92	51	26	15	
Age-adjusted HR	1.78 (1.18–2.68)**	1.39 (0.97–1.99)	1.38 (0.98–1.94)	1.00	1.15 (0.72–1.84)	1.25 (0.70–2.22)	0.002
Multivariate HR	1.63 (1.10–2.42)*	1.39 (0.97–1.98)	1.34 (0.95–1.90)	1.00	1.09 (0.67–1.77)	1.12 (0.61–2.06)	0.01
Women							
Person-year	47,300	109,129	163,942	140,420	81,282	58,292	
Myocardial infarction	34	33	52	49	40	32	
Age-adjusted HR (95% CI)	1.36 (0.88–2.12)	0.77 (0.50–1.20)	0.88 (0.59–1.30)	1.00	1.34 (0.88–2.04)	1.46 (0.94–2.29)	0.18
Multivariate HR (95% CI)	1.29 (0.83–2.00)	0.89 (0.57–1.40)	0.84 (0.55–1.28)	1.00	1.58 (1.02–2.43)*	1.25 (0.75–2.07)	0.22
Heart failure, n	51	55	72	63	32	31	
Age-adjusted HR (95% CI)	1.49 (1.02–2.16)*	0.97 (0.68–1.39)	0.93 (0.67–1.31)	1.00	0.85 (0.55–1.30)	1.11 (0.72–1.71)	0.01
Multivariate HR (95% CI)	1.93 (1.36–2.73)**	0.99 (0.68–1.45)	1.09 (0.77–1.53)	1.00	0.73 (0.45–1.17)	1.18 (0.73–1.82)	0.01
Total subjects							
Person-year	74,223	192,820	283,998	245,626	132,199	86,717	
Myocardial infarction	70	116	152	137	90	75	
Age-adjusted HR (95% CI)	1.21 (0.91–1.62)	0.92 (0.72–1.18)	0.89 (0.71–1.13)	1.00	1.30 (0.99–1.69)	1.74 (1.31–2.31)***	0.002
Multivariate HR (95% CI)	1.20 (0.91–1.60)	0.86 (0.66–1.12)	0.90 (0.71–1.15)	1.00	1.35 (1.02–1.79)*	1.68 (1.24–2.28)***	<0.001
Heart failure, n	94	129	164	114	58	46	
Age-adjusted HR (95% CI)	1.62 (1.23–2.14)***	1.16 (0.90–1.50)	1.14 (0.90–1.50)	1.00	0.98 (0.71–1.69)	1.20 (0.85–1.69)	<0.001
Multivariate HR (95% CI)	1.83 (1.41–2.37)***	1.20 (0.93–1.55)	1.22 (0.96–1.56)	1.00	0.89 (0.64–1.25)	1.17 (0.81–1.68)	<0.001

*P<0.05, **P<0.01,***P<0.001, compared to BMI =23.0–24.9 kg/m2. Multivariate adjustment: age, smoking, alcohol consumption, hours of walking and exercise, perceived mental stress, education levels, and fresh fish intake.
CAD, coronary artery disease; CI, confidence interval; HF, heart failure; HR, hazard ratio. Other abbreviation as in Table 1.

egories of baseline BMI and weight change since the subjects were 20 years of age. BMI was positively associated with alcohol consumption and fresh fish intake. BMI was inversely associated with age, current smoking, mental stress and walking in both men and women (**Table 1**). Weight gain was positively associated with mental stress in both men and women. Weight gain was inversely associated with current smoking, walking and exercise in both men and women, and also inversely associated with alcohol consumption in men (**Table 2**).

The HRs of mortality from MI and HF according to BMI category are listed in **Table 3**. Compared to subjects with BMI in the range 23.0–24.9 kg/m², both men and women with BMI ≥27.0 kg/m² had a higher age-adjusted mortality from MI, but not from HF. After adjustment for other cardiovascular risk factors, these associations did not change substantially. The multivariate HRs (95% CI) of MI associated with BMI ≥27.0 kg/m² were 2.06 (1.40–3.02) for men, 1.25 (0.75–2.07) for women and 1.68 (1.24–2.28) for all subjects. Those for HF were 1.12 (0.61–2.06) for men, 1.18 (0.73–1.82) for women and 1.17 (0.81–1.68) for all subjects. The multivariate HRs for total deaths were 1.16 (1.05–1.28) for men, 1.21 (1.10–1.33) for women and 1.19 (1.12–1.28) for all subjects (data not shown). An increased mortality from HF was observed in both men and women with BMI <19.0 kg/m². The multivariate HRs (95% CI) for HF were 1.63 (1.10–2.42) for men, 1.93 (1.36–2.73) for women and 1.83 (1.41–2.37) for all subjects. The multivariate HRs for total deaths were 1.44 (1.35–1.54) for men, 1.42 (1.30–1.55) for women and 1.44 (1.37–1.52) for all subjects (data not shown).

Table 4 lists the HRs of MI and HF according to weight change since the age of 20 years. Weight gain was associated with increased mortality from MI, whereas weight loss was associated with increased mortality from HF. Compared to subjects with no weight change (within ±5.0 kg) since 20 years of age, the multivariate HRs (95% CI) for MI for weight change +10.0 kg or more were 1.51 (1.11–2.06) for men, 1.80 (1.23–2.64) for women and 1.67 (1.32–2.12) for all subjects, whereas those for HF were 0.76 (0.51–1.13) for men, 0.94 (0.66–1.33) for women and 0.91 (0.69–1.20) for all subjects. The multivariate HRs for total deaths were 1.02 (0.94–1.10) for men, 1.15 (1.05–1.25) for women, and 1.08 (1.02–1.14) for all subjects

Table 4. Mortality From CAD and HF vs. Weight Change Since 20 Years of Age

	Weight change since 20 years of age (kg)					P for trend
	−10.0 or more	−5.0 to −9.9	−4.9 to +4.9	+5.0 to +9.9	+10.0 or more	
Men						
Person-year	25,677	59,591	170,501	80,320	79,131	
Myocardial infarction	47	84	137	56	76	
Age-adjusted HR (95% CI)	1.36 (0.97–1.91)	1.22 (0.93–1.61)	1.00	1.05 (0.77–1.43)	1.50 (1.13–1.99)**	0.84
Multivariate HR (95% CI)	0.86 (0.57–1.31)	1.21 (0.91–1.60)	1.00	1.13 (0.82–1.57)	1.51 (1.11–2.06)**	0.36
Heart failure, n	44	86	110	32	39	
Age-adjusted HR (95% CI)	1.23 (0.86–1.75)	1.34 (1.01–1.78)*	1.00	0.82 (0.55–1.22)	0.81 (0.54–1.23)	<0.001
Multivariate HR (95% CI)	1.33 (0.93–1.89)	1.33 (1.01–1.75)*	1.00	0.83 (0.57–1.20)	0.76 (0.51–1.13)	0.01
Women						
Person-year	28,098	81,313	241,854	132,833	116,267	
Myocardial infarction	21	48	85	34	52	
Age-adjusted HR (95% CI)	0.88 (0.54–1.42)	0.99 (0.69–1.42)	1.00	0.85 (0.57–1.36)	1.43 (1.01–2.02)*	0.13
Multivariate HR (95% CI)	0.90 (0.54–1.53)	1.17 (0.80–1.69)	1.00	0.88 (0.57–1.38)	1.80 (1.23–2.64)**	0.13
Heart failure, n	45	69	101	48	41	
Age-adjusted HR (95% CI)	1.44 (1.01–2.06)*	1.12 (0.83–1.53)	1.00	1.03 (0.73–1.46)	0.97 (0.67–1.39)	0.04
Multivariate HR (95% CI)	1.48 (1.04–2.12)*	1.10 (0.82–1.48)	1.00	0.92 (0.66–1.29)	0.94 (0.66–1.33)	0.04
Total subjects						
Person-year	53,774	140,904	412,355	213,152	195,398	
Myocardial infarction	68	132	222	90	128	
Age-adjusted HR (95% CI)	1.17 (0.88–1.54)	1.13 (0.91–1.40)	1.00	0.97 (0.76–1.24)	1.50 (1.20–1.86)***	0.24
Multivariate HR (95% CI)	0.88 (0.64–1.21)	1.18 (0.94–1.48)	1.00	1.06 (0.81–1.37)	1.67 (1.32–2.12)***	0.07
Heart failure, n	89	155	211	80	70	
Age-adjusted HR (95% CI)	1.34 (1.04–1.72)*	1.24 (1.01–1.53)*	1.00	0.94 (0.72–1.21)	0.90 (0.69–1.18)	<0.001
Multivariate HR (95% CI)	1.57 (1.20–2.05)**	1.33 (1.08–1.65)**	1.00	0.90 (0.68–1.18)	0.91 (0.69–1.20)	<0.001

*P<0.05, **P<0.01, ***P<0.001, compared to weight change within ±5.0 kg. Multivariate adjustment: age, smoking, alcohol consumption, hours of walking and exercise, perceived mental stress, education levels, fresh fish intake, and BMI at the age of 20.
Abbreviations as in Tables 1,3.

(data not shown). The multivariate HRs (95% CI) of MI for subjects with weight change −10.0 kg or more were 0.86 (0.57–1.31) for men, 0.90 (0.54–1.53) for women and 0.88 (0.64–1.21) for all subjects, whereas those of HF were 1.33 (0.93–1.89), 1.48 (1.04–2.12) and 1.57 (1.20–2.05), respectively. The corresponding multivariate HRs for total deaths were 1.44 (1.35–1.54), 1.42 (1.30–1.55) and 1.44 (1.37–1.52) (data not shown). There was a U-shaped association of BMI and weight change with risk for all-cause deaths.

These increased risks did not alter materially when deaths within 5 years were excluded from analysis. The multivariate HRs (95% CI) of MI-related death associated with weight gain were 1.61 (1.20–2.17) for men, 1.45 (1.00–2.11) for women, and 1.60 (1.27–2.01) for total subjects. The corresponding HRs (95% CI) of HF-associated death with weight loss were 1.30 (0.84–2.01), 1.49 (1.00–2.21), and 1.43 (1.07–1.91).

Also, the association of weight gain with risk of mortality from MI and of weight loss with risk of mortality from HF did not vary by age group (<60 and ≥60 years). The multivariate HR of MI for weight gain was 2.10 (1.46–3.03) and 1.28 (0.97–1.69; P for interaction =0.16), respectively. The respective HR of HF for weight loss was 1.73 (0.72–4.13) and 1.44 (1.10–1.87; P for interaction =0.43), respectively (data not shown).

Discussion

In this prospective study of Japanese men and women aged 40–79, we observed that subjects with BMI ≥27.0 kg/m^2 had an approximately 1.7-fold higher risk of mortality from MI, and those with BMI <19.0 kg/m^2 had an approximately 1.8-fold higher risk of mortality from HF than those with BMI in the range 23.0–24.9 kg/m^2. Subjects with a weight change of +10.0 kg or more since the age of 20 had a 1.7-fold higher risk of mortality from MI, when compared with those with no weight change since 20 years of age, whereas subjects with a weight change of −10.0 kg or more had an approximately 1.6-fold higher risk of mortality from HF.

The excess risk of mortality from CAD in men with high BMI has been investigated in previous prospective studies conducted in the USA,[1] Europe,[5,6] and Japan.[2,4] A prospective study of >1

million US subjects provided evidence that BMI ≥30 kg/m^2 compared to those with BMI in the range 23.5–24.9 kg/m^2 was associated with a 1.5–3-fold higher risk of mortality from CAD.[18]

The present finding that low BMI is associated with risk of mortality from HF is supported by patient-based prospective studies that found that obesity is inversely associated with mortality from HF.[12–14] Furthermore, a published meta-analysis of 28,209 men and women with HF found that obesity was inversely associated with mortality from cardiovascular disease.[15]

The excess risk of mortality from MI associated with weight gain is consistent with the results of previous studies conducted in the USA and Europe, which reported that men with weight gain since the age of 18 or 20 have a 1.3–1.9-fold higher risk of mortality from CAD.[5,6] A 10-year follow-up study of Japanese subjects reported that men who have weight gain since the age of 20 have a 1.4-fold higher risk of CAD than those with no weight change.[4] In contrast, several clinical studies showed that patients with cardiovascular disease or overweight with coronary risk factors who lost weight intentionally had decreased risk of CAD: the HRs were 0.57 (0.39–0.84) and 0.62 (0.42–0.92).[19,20] No previous prospective studies, however, have examined the association between weight change and risk of HF in the general population.

The present finding that subjects with low BMI or weight loss had a higher risk of mortality from HF is supported by previous findings suggesting that HF patients with a lower BMI have a higher risk of mortality.[12–14] Additionally, patients who lose weight after MI have a higher risk of mortality from cardiovascular disease.[16] Tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine, is produced by the myocardial cells under conditions of cardiac injury, such as myocardial ischemia or infarction and left ventricular pressure or volume overload.[21] Patients with chronic HF have higher TNF-α.[22] It has been shown that high TNF-α induces eating disorders and cachexia,[22–24] leading to weight loss, and that cytokines enhance heart muscle cell death, contractile dysfunction, and ventricular enlargement in the process of HF.[25–27]

The present study has several limitations. First, self-reported weight data collected from the population surveys were used for the analysis, which may lead to an underestimation of weight and an overestimation of height.[28] A previous study, however, of 1,823 Japanese men and women aged 40–68 showed that the weight estimated from self-report highly correlated with actual weight (r=0.97), and that the mean difference was small (mean±SD, 55.8±8.7 kg vs. 55.7±8.3 kg).[29] Second, we used recalled data regarding weight at 20 years of age. A validity study indicated that recalled weight at the age of 25 years strongly correlated with actual measured weight (r=0.85).[30] Third, the cause of mortality used in the present study was the underlying cause of death. Usually, subsequent development of HF after large MI could be coded as MI, but cases of long clinical course between MI and HF are more likely to be coded as HF. In addition, Japanese physicians were inclined to diagnose death of unknown origin or death occurring during the end stage of chronic disease as "unspecified HF" before 1994.[31] The association between weight loss and mortality from HF, however, did not alter materially when using congestive HF (ICD I50.0) only for analysis (no. cases =32 for men and 43 for women). The multivariate HRs of HF for weight change of −10.0 or more compared with no weight change were 1.60 (0.52–4.91) for men, 2.66 (1.14–6.22) for women and 2.12 (1.13–4.34) for total subjects (data not shown). Fourth, approximately 63% of the total participants had weight data at 20 years of age, but there were no apparent differences in age and age-adjusted means or proportions of major cardiovascular risk factors between the subjects with and without weight data at 20 years of age. Thus, selection bias may be small in the evaluation of associations between weight change and mortality.

Conclusions

High BMI and weight gain are associated with increased risk of mortality from MI, whereas low BMI and weight loss are associated with increased risk of mortality from HF. These opposing associations may suggest specific pathophysiological mechanisms characteristic of the development of MI and HF.

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Disclosures

None.

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