BMJ Open

The burden of multimorbidity across generations in Japan 2014-2019 - a historical cohort study using nationwide medical claims data

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063216
Article Type:	Original research
Date Submitted by the Author:	28-Mar-2022
Complete List of Authors:	Saito, Yoshiyuki; The University of Tokyo, Department of Health Economics & Outcomes Research; Kyoto University School of Public Health, Department of Health Informatics Igarashi, Ataru ; The University of Tokyo, Department of Health Economics & Outcomes Research; Yokohama City University School of Medicine Graduate School of Medicine, Unit of Public Health and Preventive Medicine Nakayama, Takeo; Kyoto University School of Public Health, Department of Health Informatics Fukuma, Shingo; Kyoto University, Department of Human Health Sciences
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

The burden of multimorbidity across generations in Japan 2014-2019 - a historical cohort study using nationwide medical claims data

Authors

Yoshiyuki Saito[1,2*] PharmD, Ataru Igarashi[1,3] PhD, Takeo Nakayama[2] MD PhD, Shingo Fukuma[4] MD

Author Affiliations

[1]Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[2]Department of Health Informatics, School of Public Health, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

[3]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa 236-0027, Japan

[4]School of Human Health Sciences, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

Running head

The burden of multimorbidity in Japan 2014-2019

*Corresponding author

Yoshiyuki Saito, PharmD

Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

E-mail: saito.yoshiyuki.86x@kyoto-u.jp

Tel: +81-3-5841-4828

Word count: 3121 (incl. abstract)

Tables: 1

Figures: 3

Supplementary Tables: 4

Abstract

Objective

To describe the prevalence of multimorbidity and its associations with clinical outcomes across age groups.

Design

Historical cohort study using nationwide medical claims data.

Setting

Carried out in Japan between April 2014 and March 2019.

Participants

N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE) were included into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals were included into the cohort data set spanning FY2014-FY2018.

Exposures

Multimorbidity was defined as having ≥2 of 15 chronic conditions according to the ICD-10 codes of the Charlson Comorbidity Index.

Primary and Secondary Outcomes

Primary outcome: The standardised prevalence of multimorbidity across age groups was evaluated using data from FY 2014 and extrapolated to the Japanese total population. Secondary Outcome: Hospitalisation and death events were traced by month using medical claims data and insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation and/or death events across age groups were analysed using a Cox regression model.

Results

The standardised prevalence of multimorbidity was approximately 5% (ages 20-29), 10% (30-39), 20% (40-49), 30% (50-59), 50% (60-69), and 60% (70-74). Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity had a higher incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41 [95% CI, 3.23-3.53] in ages ≥60). The difference in the incidence of clinical events between multimorbidity and no-multimorbidity was larger than that between age groups.

Conclusions

Multimorbidity is already prevalent in the middle-aged generation and is associated with poor clinical outcomes. These findings underscore the significance of multimorbidity and highlight the urgent need for preventive intervention at the public health care level.

5

72

Article Summary

Strengths and limitations of this study

- The current study covers a wide age range of individuals from a nationwide general population.
- Japan`s high medical insurance coverage rate made it possible to comprehensively identify chronic diseases from receipts.
- Longitudinal analysis enabled the examination of clinical outcomes of multiple co-morbidities.
- The prevalence of multimorbidity may be underestimated because the target population comprised regular employees and their families and might accordingly be healthier than the general population.

Keywords

chronic disease, insurance claims, middle age, multimorbidity, preventive medicine

Introduction

Aging societies worldwide face the problem of how to provide adequate and affordable health care for a growing number of patients with multiple chronic conditions, termed multimorbidity.[1,2] Managing multimorbidity is becoming a global challenge on the clinical and public healthcare level not only in high-, but also in low- and middle-income countries.[3] Many epidemiological studies on multimorbidity have shown its association with age, socio-demographic and socio-economic factors.[4-7] In addition, numerous studies have shown that multiple comorbidities are common in older people.[8-11] It has been reported that multimorbid older patients had more than twice as many contacts per year with physicians than those without multimorbidity[12] and that the likelihood of being hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.[8] On the other hand, the accumulation of chronic diseases occurs continuously from middle age. A number of recent studies conducted in various countries have reported that the onset of multimorbidity is shifting towards younger age groups.[6, 13-15] However, multimorbidity studies tend to focus on older people, and in-depth knowledge on multimorbidity in younger age groups is lacking.

Here, to evaluate the current status of multimorbidity across age groups and examine its association with clinical outcomes, we analysed a large nationwide medical claims

cohort. Our findings add to existing knowledge by showing that multimorbidity has a significant impact on health starting from middle age and underscore the need for preventive intervention on the public health care level.

Materials and Methods

Data source

We used the nationwide medical claims and enrolment data of the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE), which is one of the largest social insurance associations in Japan. HIA^{2}CE is a comprehensive insurer which includes 1700 companies, from small engineering companies to middle and large construction companies across Japan. This claims database covers a total of 400 000 insured persons, consisting of employees and their dependents.

Japan has maintained a universal health coverage system since 1961. All medical information regarding clinical practice covered by this health insurance is included in the medical claims data, except for self-financed medical care and individuals who receive public assistance. Furthermore, medical facilities have been obliged since 2011 to submit medical claims data as an electronic record. Medical claims data include the names of the diagnosed diseases, the names of medical procedures, and the names of prescribed medications, among others. In the present study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and hospitalisations and deaths from the medical claims data in HIA^{2}CE from FY2014 to FY2018 (April 2014 to March 2019).

The enrolment data from HIA^{2}CE includes the medical characteristics of insured persons as of April 2019.

Research design and study population

We prepared two data sets for analysis. The first data set contained baseline data of FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The study population for this baseline data set included individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Participants younger than 20 and older than 75 years in FY2014 as well as participants who died during FY2014 were excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to FY2018 (April 2014 to March 2019). We used this cohort data set to conduct Cox regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).

Definition of diagnosed diseases and multimorbidity

The Charlson Comorbidity Index (CCI) is a validated tool which has been widely used to assess patient comorbidities.[16] The CCI Canadian version has been reported to be applicable to Japanese claims data.[17] We therefore defined diagnosed diseases using medical claims data following ICD-10 codes of the CCI Canada version. We merged the

conditions “diabetes with chronic complication” and “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease” and “moderate or severe liver disease” into “liver disease”. The following 15 chronic conditions were included: AIDS/HIV, any malignancy (including lymphoma and leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour, liver disease, myocardial infarction, peptic ulcer disease, renal disease, and rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in the Supplement. Multimorbidity status was defined as the concurrent presence of two or more (≥2) diagnosed diseases among these conditions.[18,19]

Definition of outcome events; hospitalisation and death

We defined two composite outcomes, hospitalisation and death, which occurred during the period from FY2015 to FY2018. Using the medical claims data, both events were traced by month. In Japan, the validity of death event information is reported to be less sensitive if derived from medical claims data only.[20,21] Therefore, we also used death information from enrolment data recorded by the insurer: if either contained death information, this was defined as a death event.

Estimation of diagnosed disease prevalence to nationwide scale

Diagnosed disease prevalence from baseline data was standardised to the nationwide Japanese total population. We calculated diagnosed disease prevalence according to 5-year age brackets and gender and applied it to the same age and gender groups of the vital statistics 2014 in Japan.[22]

Effect of multimorbidity by age group

To examine the effect of multimorbidity by age group, we performed Cox regression analysis using cohort data from four consecutive years (FY2015 to FY2018). To examine the independent and additive effect of multimorbidity and aging, we defined combined categories according to three age groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥60, respectively) and the binary status of multimorbidity, with the reference set as no multimorbidity individuals aged 20-39.

Statistical analysis

Effects of multimorbidity by age groups were analysed using Cox regression as described under the heading “Effect of multimorbidity by age group”. Results were

considered statistically significant at a two-sided *P*-value of less than 0.05. All analyses were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX, USA).

Patient and Public involvement

Patients or the public were not involved in this research. However, the results of this study will be disseminated to the public through various means including published papers and presentations.

Results

Study participants

We analysed *n* = 246 671 individuals in the baseline data set in FY2014 and *n* = 181 959 individuals in the cohort data set FY2014-FY2018. Because follow-up was four years, the cohort data set was slightly smaller than the baseline data set, especially as a number of young individuals aged 20-24 and older individuals aged >60 dropped out. This may be due to raising children or early retirement, and explains the higher proportion of men in the cohort data set. Mean age and co-morbidity numbers among CCI diseases were mostly comparable between the two data sets, although the prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in disease prevalence between genders were observed. Notably, men had a higher prevalence of diabetes mellitus (*P* = 0.001) whereas women had a higher prevalence of chronic pulmonary disease (*P* = 0.002).

Estimated prevalence of multimorbidity in the Japanese total population

The prevalence of diagnosed diseases in FY2014 was applied to the vital statistics of the Japanese population in 2014. The standardised prevalence of multimorbidity was

estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population (Table 1). The prevalence of multimorbidity increased with age, i.e., 25-24 (3.9%), 25-29 (7.7%), 30-34 (9.7%), 35-39 (12.5%), 40-44 (14.6%), 45-49 (19.0%), 50-54 (25.9%), 55-59 (33.2%), 60-64 (40.7%), 65-69 (49.9%), and 70-74 (60.1%) (Fig. 2A). Figure 2B shows the types of disease and their prevalence across age groups. The top five diseases across the age groups “young” (20-39), “middle-age (40-59), and “old” (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, and any malignancy; “middle-age”: chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up across the age groups from ranking fourth to first. Details of the prevalence of specific diseases are shown in eTable 3 in the Supplement. In Figure 2C, disease prevalence is shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-44, the top five accelerating diseases were dementia, cerebrovascular disease, peripheral vascular disease, metastatic tumour, and congestive heart failure.

Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population

	Baseline data in FY2014						Japanese total population					
	Overall		Men		Women		Overall		Men		Women	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%	*N*=88,923,000	%	*N*=44,288,000	%	*N*=44,640,000	%
Men	144,237	58.5	-	-	-	-	44,288,000	49.8	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8	48.0	15.3	47.7	15.3	48.4	15.4
20-24	18,524	7.5	11,315	7.8	7,209	7.0	6,203,000	7.0	3,192,000	7.2	3,012,000	6.7
25-29	17,251	7.0	12,014	8.3	5,237	5.1	6,677,000	7.5	3,414,000	7.7	3,264,000	7.3
30-34	18,093	7.3	11,104	7.7	6,989	6.8	7,466,000	8.4	3,788,000	8.6	3,680,000	8.2
35-39	23,878	9.7	13,278	9.2	10,600	0.3	8,670,000	9.8	4,394,000	9.9	4,276,000	9.6
40-44	39,721	16.1	21,640	15.0	18,081	17.7	9,793,000	11.0	4,956,000	11.2	4,837,000	10.8
45-49	40,908	16.6	24,191	16.8	16,717	16.3	8,609,000	9.7	4,329,000	9.8	4,278,000	9.6
50-54	29,466	11.9	17,577	12.2	11,889	11.6	7,790,000	8.8	3,903,000	8.8	3,887,000	8.7
55-59	20,149	8.2	11,343	7.9	8,806	8.6	7,653,000	8.6	3,802,000	8.6	3,853,000	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4	8,979,000	0.1	4,406,000	9.9	4,573,000	10.2
65-69	11,931	4.8	6,768	4.7	5,163	5.0	9,155,000	10.3	4,414,000	10.0	4,741,000	10.6
70-74	5,472	2.2	2,301	1.6	3,171	3.1	7,928,000	8.9	3,690,000	8.3	4,239,000	9.5
AIDS/HIV	96	0.0	62	0.0	34	0.0	34,034	0.0	18,979	0.0	15,055	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3	5,775,260	6.5	2,668,349	6.0	3,106,911	7.0
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3	5,773,295	6.5	3,023,765	6.8	2,749,530	6.2
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2	17,303,735	19.5	7,713,864	17.4	9,589,871	21.5
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9	4,317,076	4.9	2,459,170	5.6	1,857,906	4.2
Dementia	447	0.2	210	0.1	237	0.2	410,326	0.5	179,350	0.4	230,976	0.5
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2	12,689,040	14.3	7,122,240	16.1	5,566,801	12.5
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3	424,609	0.5	253,040	0.6	171,569	0.4
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9	11,341,444	2.8	6,031,029	13.6	5,310,415	11.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2	1,235,336	1.4	598,734	1.4	636,601	1.4
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3	769,977	0.9	575,894	1.3	194,083	0.4
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3	11,238,524	12.6	5,485,994	12.4	5,752,530	12.9
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6	5,197,644	5.8	2,503,359	5.7	2,694,285	6.0
Renal disease	2,573	1.0	1,751	1.2	822	0.8	1,261,138	1.4	784,770	1.8	476,367	1.1
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7	1,928,685	2.2	530,072	1.2	1,398,613	3.1
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3	30,041,150	33.8	14,676,045	33.1	15,365,106	34.4
Co-morbidity no. among CCI diseases												
no disease	171,140	69.4	101,857	70.6	69,283	67.6	57,293,691	64.4	29,006,814	65.5	28,286,877	63.4
1 disease	22,947	9.3	12,032	8.3	10,915	10.7	8,464,436	9.5	3,702,220	8.4	4,762,216	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9	6,799,080	7.6	3,029,535	6.8	3,769,544	8.4
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4	5,534,827	6.2	2,652,231	6.0	2,882,596	6.5
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6	4,261,753	4.8	2,242,062	5.1	2,019,691	4.5
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7	6,574,213	7.4	3,655,138	8.3	2,919,075	6.5

Values are numbers (%) unless otherwise stated.

[a] Any malignancy includes leukemia and lymphoma.

FY; fiscal year

SD; standard deviation

CCI; Charlson Comorbidity Index

Effect of multimorbidity by age group

Cox regression analysis showed that young individuals aged 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages ≥60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59 without multimorbidity) (Fig. 3). We also assessed HRs for non-multimorbid and multimorbid women and men separately and found that women had a lower HR than men in the 20-39 age group but a higher HR than men in the ≥60 age group (eTable 4 in the Supplement).

Discussion

In this study we analysed nationwide medical claims data for 15 chronic diseases in a large cohort of the general population of Japan. As key findings, standardised prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for women. Further, age group-specific prevalence rates for multimorbidity ranged from 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an accelerating increase after age 40. Importantly, significant differences in the clinical outcomes of multimorbidity versus no multimorbidity were already present in young and middle-aged individuals.

The present study drew individuals covering a wide age range from a nationwide general population. This allowed us to examine the burden of multiple co-morbidities in young, middle-aged and old age groups in the real world. In addition, because Japan has a high medical insurance coverage rate, it was possible to comprehensively identify chronic diseases from receipts. Further, longitudinal analysis enabled us to examine the clinical outcomes of multiple co-morbidities. With regard to limitations, the target population comprised regular employees and their families and might accordingly be healthier than the general population. Also, we did not consider the presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in

individuals already suffering from other chronic diseases,[23,24] younger people,[25] and people with a low socio-economic status.[26] Such diseases often remain undiagnosed or underreported in health records.[27] These limitations likely contributed to an underestimation of multimorbidity in our cohort. Further, because we did not manually verify the presence of disease using the physician's medical records data or medication information, disease names extracted from the medical claims data might be incorrect in some cases. In particular, Japanese physicians sometimes change the name of the disease in the medical record to the "correct" disease name for the medication they wish to prescribe, a practice called "disease name for claims data".

Because of differences in data sources and study populations, direct comparison of population-based prevalence rates between studies is not straightforward. Nonetheless, the standardised prevalence rates for multimorbidity as reported in the present study - 26.1% for men and 26.0% for women - are similar to those reported by recent studies in other high-income countries, such as the United States (25% in men, 25% in women),[28] England (24.4% in men, 30% in women),[26] Canada (24.3% whole population),[5] and Denmark (19.3% in men, 23.7% in women).[6] Many previous studies on multimorbidity focused on the older generation, aged 65 and up, because of the larger number of chronic diseases in this age group and the increasing number of people entering it.

However, our present data show that already approximately 10% of 30-34-, 19% of 45-49-, and 33% of 55-59-year-olds have ≥2 chronic diseases. Further, 1% of 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥5 chronic diseases. These results show that multimorbidity is already prominent in the middle-aged population. Recent studies reported similar or slightly higher prevalence rates for ≥2 chronic diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)[25] and a Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)[5] population, although these two studies also included mental diseases and osteoporosis, which our present study did not. Our present study shows that, among 15 chronic diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes mellitus, prevalence in the present study is similar to that previously reported in an American population (15-30% in individuals aged 55-65)[25] but higher than that in a Canadian population (16.6% in individuals aged 55-64)[4]. The prevalence of chronic pulmonary disease in our present 55-65-year-olds was almost twice as high as those seen for the combined prevalence of asthma and chronic obstructive pulmonary disease (COPD) in an American population aged 55-65 years (5% for men and 10% for women)[25] and in a Canadian population

aged 55-64 years (13.7%).[5] This difference might have arisen due to our inclusion of various other pulmonary diseases besides asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in the present study was comparable to that seen in an adult population in Northern Italy[29] and in an adult population in Korea,[30] although this comparison requires care since the types of liver disease in these studies and the age groups included vary.

Analysis of clinical outcomes using Cox regression revealed that the presence of multimorbidity increased HRs in all age groups, including young individuals. In addition, comparison of the increased HRs resulting from multimorbidity versus no multimorbidity showed that the impact of multimorbidity exceeds that of increasing age. These results indicate that multimorbidity places a burden on all age groups.

Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and any malignancy) in the present study are lifestyle-related diseases that develop slowly over time. This trend should be greeted with alarm. We trust that this study raises awareness of the potential health risks and burden associated with the early onset of multimorbidity in young and middle-age, the period when one is busy working and raising children. Future studies should investigate the specific lifestyle factors associated with an elevated risk of multimorbidity

in the Japanese working population. Ultimately, public health care policies should be aimed at efforts to reverse the trend toward early multimorbidity onset.

In conclusion, the present study revealed that the impact of multimorbidity is already prominent in middle-aged Japanese, with elevated adverse events such as hospitalisation and death. In addition, the risk posed by multimorbidity exceeds that of aging in all age groups. These results underscore the need to undertake healthcare intervention against the onset of multimorbidity before middle-age, and not to leave it as a problem for geriatricians.

Ethical Approval

The present study was approved by the Institutional Review Board (IRB) of Kyoto University (approval number: R0817). All data were anonymised before analysis and none of the researchers had access to patient-identifiable information. The IRB waived informed consent for this observational study.

Data Availability Statement

All data are incorporated into the article and its online supplementary material.

Author Contributions

Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS. Administrative, technical, or material support: YS, SF. Study supervision: SF, TN. YS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval and agreed to be accountable for all aspects of work.

Acknowledgements

The authors are grateful to HIA^{2}CE for providing data for the present study.

Funding

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in the design of the study; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Competing Interests

None declared.

Patient Consent for Publication

Not applicable.

References

1 Bleich SN, Sherrod C, Chiang A, *et al*. Systematic Review of Programs Treating High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities in the United States, 2008-2014. *Prev Chronic Dis*. Nov 12 2015;12:E197. doi:10.5888/pcd12.150275

2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. *Prev Med Rep*. Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008

3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y, Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614. doi:10.1371/journal.pone.0243614

4 Low LL, Kwan YH, Ko MSM, *et al*. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245. doi:10.1001/jamanetworkopen.2019.15245

5 Pefoyo AJ, Bronskill SE, Gruneir A, *et al*. The increasing burden and complexity of multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-1733-2

6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8

7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of multimorbidity on healthcare utilisation and work productivity by socioeconomic groups: Cross-sectional analyses of Australia and Japan. *PLoS One*. 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281

8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. *BMC Health Serv Res*. Jan 22 2015;15:23. doi:10.1186/s12913-015-0698-2

9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-sectional study based on nationwide claims data. *BMJ Open*. Jun 9 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333

10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812. doi:10.1136/bmjopen-2016-012812

11 Picco L, Achilla E, Abdin E*, et al*. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10 2016;16:173. doi:10.1186/s12913-016-1421-7

12 van den Bussche H, Schon G, Kolonko T*, et al*. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54

13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152. doi:10.1186/s12916-017-0913-6

14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising burden of multimorbidity and related socio-demographic factors: a repeated cross-sectional study of Ontarians. *Can J Public Health*. Apr 13 2021;doi:10.17269/s41997-021-00474-y

15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England, 2002-2015. *J Comorb*. Jan-Dec 2019;9:2235042X19872030. doi:10.1177/2235042X19872030

16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-8

17 Quan H, Li B, Couris CM*, et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

18 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*. Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098

19 Le Reste JY, Nabbe P, Manceau B*, et al*. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001

20 Ooba N, Setoguchi S, Ando T*, et al*. Claims-based definition of death in Japanese claims database: validity and implications. *PLoS One*. 2013;8(5):e66116. doi:10.1371/journal.pone.0066116

21 Sakai M, Ohtera S, Iwao T*, et al*. Validation of claims data to identify death among aged persons utilizing enrollment data from health insurance unions. *Environ Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3

22 Statistics Bureau of Japan. Preliminary count of the Japanese population. Accessed March, 2014. http://www.stat.go.jp/data/jinsui/index.html

23 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234

24 Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002

25 Rocca WA, Boyd CM, Grossardt BR, *et al*. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49. doi:10.1016/j.mayocp.2014.07.010

26 Cassell A, Edwards D, Harshfield A, *et al*. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. Apr 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465

27 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al*. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251

28 St Sauver JL, Boyd CM, Grossardt BR, *et al*. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413

29 Bellentani S, Tiribelli C, Saccoccio G, *et al*. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec 1994;20(6):1442-9. doi:10.1002/hep.1840200611

30 Park SH, Plank LD, Suk KT, *et al*. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr 2020;26(2):209-215. doi:10.3350/cmh.2019.0065

Figure Legends

Figure 1. Participant selection flowchart. FY; fiscal year

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A**) Percentage of the population having 0 to ≥5 chronic diseases by age group. **B**) Prevalence of the top ten chronic diseases by age group. **C**) The top ten chronic diseases with the steepest increase after age 40-44 years.

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

Supplementary Information

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation and death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

483

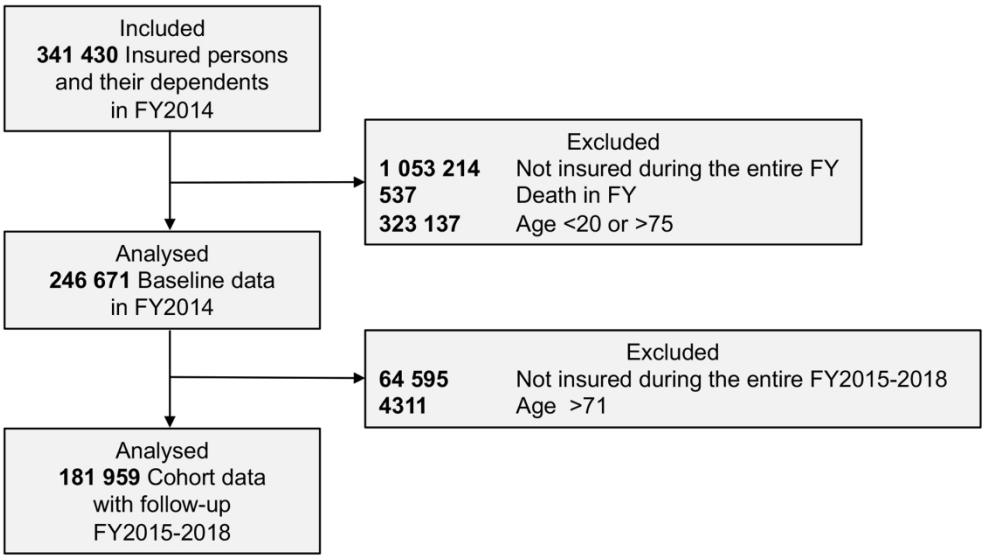

Figure 1. Participant selection flowchart. FY; fiscal year

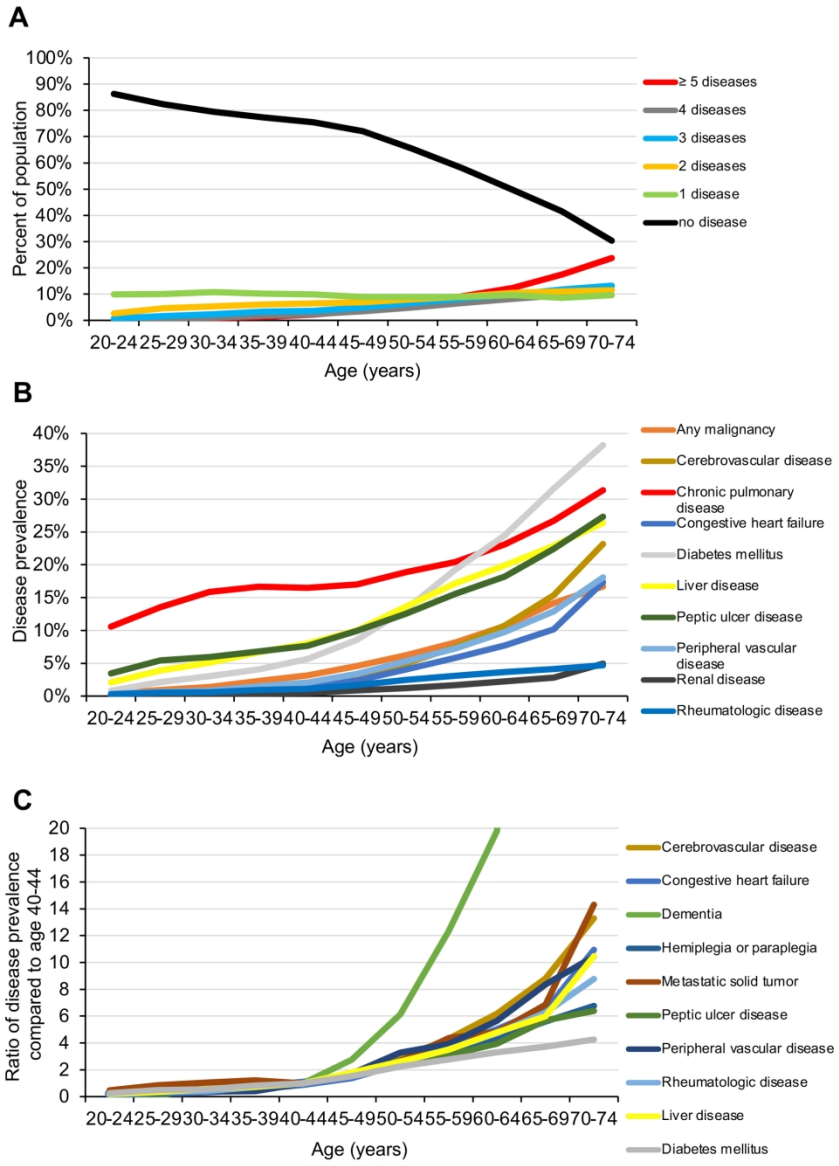

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A**) Percentage of the population having 0 to ≥5 chronic diseases by age group. **B**) Prevalence of the top ten chronic diseases by age group. **C**) The top ten chronic diseases with the steepest increase after age 40-44 years.

161x230mm (300 x 300 DPI)

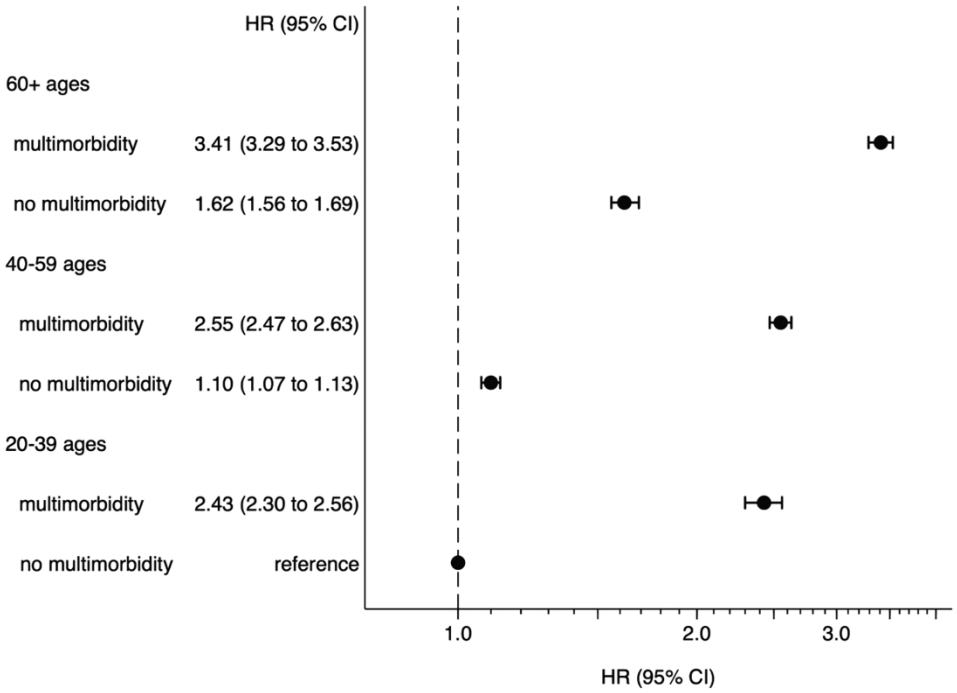

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

139x103mm (600 x 600 DPI)

Supplementary material

Title: The burden of multimorbidity across generations in Japan 2014-2019 - a historical cohort study using nationwide medical claims data

Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation and death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Diseases	ICD-10 codes
AIDS/HIV	B20.x-B22.x, B24.x
Any malignancy, incl. leukemia and lymphoma	C00.x-C26.x, C30.x-C34.x, C37.x-C41x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.3, C88.7, C88.9, C90.0, C90.1, C91.x- C93.x, C94.0-C94.3, C94.5, C94.7, C95.x, C96.x, C43.x, C88.0-C88.2, C90.2, C94.4, C97.x
Cerebrovascular disease	I69.x, G45.x, G46.x, H34.0, I60.x-I68.x
Chronic pulmonary disease	J41.x-J47.x, J60.x-J66.x, I27.8, I27.9, J40.x, J67.x, J68.4, J70.1, J70.3
Congestive heart failure	I50.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5- I42.9, I43.x, P29.0
Dementia	F00.x-F02.x, F03.x, F05.1, G30.x, G31.1
Diabetes with chronic complication	E10.2-E10.4, E11.2-E11.4, E13.2-E13.4, E14.2-E14.4, E10.5, E10.7, E11.5, E11.7, E12.2-E12.5, E12.7, E13.5, E13.7, E14.5, E14.7
Diabetes without chronic complication	E10.1, E10.9, E11.1, E11.9, E13.1, E13.9, E14.1, E14.9, E10.0, E10.6, E10.8, E11.0, E11.6, E11.8, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.6, E13.8, E14.0, E14.6, E14.8
Hemiplegia or paraplegia	G81.x, G82.0-G82.2, G04.1, G11.4, G80.1, G80.2, G82.3-G82.5, G83.0-G83.4, G83.9
Metastatic solid tumor	C77.x-C79.x, C80.x
Mild liver disease	K70.3, K71.7, K73.x, K74.3- K74.6, B18.x, K70.0-K70.2, K70.9, K71.3-K71.5, K74.0-K74.2, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	K72.1, K72.9, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K76.5
Myocardial infarction	I25.2, I21.x, I22.x
Peptic ulcer disease	K25.4-K25.7, K26.4-K26.7, K27.4-K27.7, K28.4-K28.7, K25.0-K25.3, K25.9, K26.0-K26.3, K26.9, K27.0-K27.3, K27.9, K28.0-K28.3, K28.9
Peripheral vascular disease	I71.x, I73.9, Z95.8, Z95.9, I70.x, I73.1, I73.8, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9
Renal disease	N18.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Rheumatology disease	M05.x, M06.0, M32.x, M33.2, M34.x, M35.3, M06.1-M06.4, M06.8, M06.9, M31.5, M33.0, M33.1, M33.9, M35.1, M36.0

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

	Baseline data in FY2014		Cohort data		*P*-value[c]
N	242,360	(100%)	181,959	(100%)	
Men	142,471	(58.8%)	111,088	(61.1%)	<0.01
Age (Mean, SD)	44.5	(12.5)	44.7	(10.6)	<0.01
20-24	18,524	(7.6%)	5,052	(2.8%)	<0.01
25-29	17,251	(7.1%)	12,675	(7.0%)	
30-34	18,093	(7.5%)	14,784	(8.1%)	
35-39	23,878	(9.9%)	20,508	(11.3%)	
40-44	39,721	(16.4%)	35,168	(19.3%)	
45-49	40,908	(16.9%)	37,124	(20.4%)	
50-54	29,466	(12.2%)	25,906	(14.2%)	
55-59	20,149	(8.3%)	13,052	(7.2%)	
60-64	21,278	(8.8%)	10,735	(5.9%)	
65-69	11,931	(4.9%)	6,246	(3.4%)	
70-71	1,161	(0.5%)	709	(0.4%)	
AIDS/HIV	94	(0.0%)	74	(0.0%)	0.76
Any malignancy[a]	11,343	(4.7%)	8,377	(4.6%)	0.24
Cerebrovascular disease	9,860	(4.1%)	6,971	(3.8%)	<0.01
Chronic pulmonary disease	41,866	(17.3%)	32,093	(17.6%)	<0.01
Congestive heart failure	7,751	(3.2%)	5,710	(3.1%)	0.27
Dementia	291	(0.1%)	190	(0.1%)	0.13
Diabetes mellitus	25,716	(10.6%)	18,755	(10.3%)	<0.01
Hemiplegia or paraplegia	729	(0.3%)	507	(0.3%)	0.19
Liver disease	25,999	(10.7%)	19,725	(10.8%)	0.24
Metastatic solid tumor	2,381	(1.0%)	1,823	(1.0%)	0.53
Myocardial infarction	1,526	(0.6%)	1,092	(0.6%)	0.22
Peptic ulcer disease	24,859	(10.3%)	18,594	(10.2%)	0.68
Peripheral vascular disease	9,623	(4.0%)	7,083	(3.9%)	0.20

	Baseline data in FY2014		Cohort data		*P*-value[c]
N	242,360	(100%)	181,959	(100%)	
Renal disease	2,350	(1.0%)	1,747	(1.0%)	0.75
Rheumatologic disease	3,931	(1.6%)	2,926	(1.6%)	0.72
At least one disease among the top five[b]	69,014	(28.5%)	50,660	(27.8%)	<0.01
Co-morbidity no. among CCI diseases (Mean, SD)	0.8	(1.6)	0.8	(1.6)	0.16
0 disease	169,872	(70.1%)	129,037	(70.9%)	<0.01
1 disease	22,514	(9.3%)	15,532	(8.5%)	
2 diseases	16,605	(6.9%)	12,375	(6.8%)	
3 diseases	12,242	(5.1%)	9,046	(5.0%)	
4 diseases	9,076	(3.7%)	6,816	(3.7%)	
5 diseases	12,051	(5.0%)	9,153	(5.0%)	
Composite outcomes	36,893	(15.2%)	31,224	(17.2%)	<0.01
Death	1,507	(0.6%)	1,507	(0.8%)	
Hospitalisation	36,495	(15.1%)	30,826	(16.9%)	

[a] Any malignancy includes leukemia and lymphoma.

[b] Top 5 diseases include chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and cerebrovascular disease.

SD; standard deviation, CCI; Charlson Comorbidity Index
[c] Age (Mean) and Co-morbidity no. (Mean): Student`s t-test. All other variables: Pearson's chi-square test.

Supplementary eTable 3. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		20-24		25-29		30-34	
	88,923,000	(100%)	6,204,000	(100%)	6,678,000	(100%)	7,468,000	(100%)
Men	44,288,000	(49.8%)	3,192,000	(51.5%)	3,414,000	(51.1%)	3,788,000	(50.7%)
AIDS/HIV	34,034	(0.0%)	1,400	(0.0%)	1,137	(0.0%)	1,394	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	24,047	(0.4%)	60,604	(0.9%)	103,907	(1.4%)
Cerebrovascular disease	5,773,295	(6.5%)	12,484	(0.2%)	23,767	(0.4%)	40,440	(0.5%)
Chronic pulmonary disease	17,303,735	(19.5%)	656,012	(10.6%)	901,156	(13.5%)	1,184,702	(15.9%)
Congestive heart failure	4,317,076	(4.9%)	21,322	(0.3%)	34,950	(0.5%)	52,469	(0.7%)
Dementia	410,326	(0.5%)	418	(0.0%)	0	(0.0%)	1,053	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	50,290	(0.8%)	141,852	(2.1%)	228,348	(3.1%)
Hemiplegia or paraplegia	424,609	(0.5%)	3,782	(0.1%)	7,489	(0.1%)	10,227	(0.1%)
Liver disease	11,341,444	(12.8%)	129,091	(2.1%)	259,190	(3.9%)	380,993	(5.1%)
Metastatic solid tumor	1,235,336	(1.4%)	6,706	(0.1%)	9,643	(0.1%)	15,804	(0.2%)
Myocardial infarction	769,977	(0.9%)	3,510	(0.1%)	3,859	(0.1%)	7,438	(0.1%)
Peptic ulcer disease	11,238,524	(12.6%)	213,860	(3.4%)	364,164	(5.5%)	444,445	(6.0%)
Peripheral vascular disease	5,197,644	(5.8%)	20,276	(0.3%)	42,759	(0.6%)	60,055	(0.8%)
Renal disease	1,261,138	(1.4%)	6,164	(0.1%)	11,118	(0.2%)	19,957	(0.3%)
Rheumatologic disease	1,928,685	(2.2%)	17,602	(0.3%)	35,051	(0.5%)	43,777	(0.6%)
no disease	57,293,691	(64.4%)	5,352,990	(86.3%)	5,500,039	(82.4%)	5,935,225	(79.5%)
1 disease	8,464,436	(9.5%)	609,768	(9.8%)	666,087	(10.0%)	805,022	(10.8%)
2 diseases	6,799,080	(7.6%)	163,269	(2.6%)	310,407	(4.6%)	399,222	(5.3%)
3 diseases	5,534,827	(6.2%)	45,066	(0.7%)	104,758	(1.6%)	178,423	(2.4%)
4 diseases	4,261,753	(4.8%)	19,190	(0.3%)	52,301	(0.8%)	77,876	(1.0%)
≥ 5 diseases	6,574,213	(7.4%)	13,716	(0.2%)	44,409	(0.7%)	72,233	(1.0%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		35-39		40-44		45-49	
	88,923,000	(100%)	8,670,000	(100%)	9,793,000	(100%)	8,607,000	(100%)
Men	44,288,000	(49.8%)	4,394,000	(50.7%)	4,956,000	(50.6%)	4,329,000	(50.3%)
AIDS/HIV	34,034	(0.0%)	4,592	(0.1%)	4,124	(0.0%)	3,069	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	198,069	(2.3%)	308,591	(3.2%)	393,299	(4.6%)
Cerebrovascular disease	5,773,295	(6.5%)	93,413	(1.1%)	170,645	(1.7%)	265,098	(3.1%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,446,109	(16.7%)	1,613,639	(16.5%)	1,462,084	(17.0%)
Congestive heart failure	4,317,076	(4.9%)	90,394	(1.0%)	155,193	(1.6%)	201,862	(2.3%)
Dementia	410,326	(0.5%)	734	(0.0%)	1,490	(0.0%)	3,606	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	352,333	(4.1%)	553,455	(5.7%)	737,731	(8.6%)
Hemiplegia or paraplegia	424,609	(0.5%)	13,621	(0.2%)	12,793	(0.1%)	19,669	(0.2%)
Liver disease	11,341,444	(12.8%)	577,316	(6.7%)	784,095	(8.0%)	858,769	(10.0%)
Metastatic solid tumor	1,235,336	(1.4%)	29,912	(0.3%)	56,656	(0.6%)	78,055	(0.9%)
Myocardial infarction	769,977	(0.9%)	8,925	(0.1%)	25,198	(0.3%)	37,793	(0.4%)
Peptic ulcer disease	11,238,524	(12.6%)	589,633	(6.8%)	749,581	(7.7%)	856,494	(10.0%)
Peripheral vascular disease	5,197,644	(5.8%)	127,339	(1.5%)	201,866	(2.1%)	288,167	(3.3%)
Renal disease	1,261,138	(1.4%)	30,634	(0.4%)	46,209	(0.5%)	73,397	(0.9%)
Rheumatologic disease	1,928,685	(2.2%)	79,300	(0.9%)	108,081	(1.1%)	143,756	(1.7%)
no disease	57,293,691	(64.4%)	6,707,086	(77.4%)	7,389,249	(75.5%)	6,205,507	(72.1%)
1 disease	8,464,436	(9.5%)	879,686	(10.1%)	969,263	(9.9%)	762,446	(8.9%)
2 diseases	6,799,080	(7.6%)	529,075	(6.1%)	633,182	(6.5%)	588,650	(6.8%)
3 diseases	5,534,827	(6.2%)	284,566	(3.3%)	352,334	(3.6%)	416,546	(4.8%)
4 diseases	4,261,753	(4.8%)	152,965	(1.8%)	232,087	(2.4%)	297,143	(3.5%)
≥ 5 diseases	6,574,213	(7.4%)	116,621	(1.3%)	216,885	(2.2%)	336,707	(3.9%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		50-54		55-59		60-64	
	88,923,000	(100%)	7,790,000	(100%)	7,655,000	(100%)	8,979,000	(100%)
Men	44,288,000	(49.8%)	3,903,000	(50.1%)	3,802,000	(49.7%)	4,406,000	(49.1%)
AIDS/HIV	34,034	(0.0%)	2,979	(0.0%)	3,324	(0.0%)	5,281	(0.1%)
Any malignancy[a]	5,775,260	(6.5%)	483,592	(6.2%)	624,101	(8.2%)	958,696	(10.7%)
Cerebrovascular disease	5,773,295	(6.5%)	387,663	(5.0%)	573,513	(7.5%)	965,151	(10.7%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,469,169	(18.9%)	1,565,078	(20.4%)	2,074,822	(23.1%)
Congestive heart failure	4,317,076	(4.9%)	316,491	(4.1%)	443,956	(5.8%)	694,542	(7.7%)
Dementia	410,326	(0.5%)	7,254	(0.1%)	14,375	(0.2%)	27,048	(0.3%)
Diabetes mellitus	12,689,040	(14.3%)	1,028,899	(13.2%)	1,477,049	(19.3%)	2,197,472	(24.5%)
Hemiplegia or paraplegia	424,609	(0.5%)	26,826	(0.3%)	43,702	(0.6%)	56,416	(0.6%)
Liver disease	11,341,444	(12.8%)	1,063,948	(13.7%)	1,316,086	(17.2%)	1,785,515	(19.9%)
Metastatic solid tumor	1,235,336	(1.4%)	104,654	(1.3%)	136,279	(1.8%)	204,377	(2.3%)
Myocardial infarction	769,977	(0.9%)	65,457	(0.8%)	76,970	(1.0%)	130,757	(1.5%)
Peptic ulcer disease	11,238,524	(12.6%)	977,192	(12.5%)	1,190,533	(15.6%)	1,633,285	(18.2%)
Peripheral vascular disease	5,197,644	(5.8%)	411,839	(5.3%)	554,776	(7.2%)	876,673	(9.8%)
Renal disease	1,261,138	(1.4%)	95,578	(1.2%)	126,432	(1.7%)	202,057	(2.3%)
Rheumatologic disease	1,928,685	(2.2%)	191,910	(2.5%)	235,332	(3.1%)	326,918	(3.6%)
no disease	57,293,691	(64.4%)	5,087,646	(65.3%)	4,435,684	(57.9%)	4,468,987	(49.8%)
1 disease	8,464,436	(9.5%)	687,805	(8.8%)	680,727	(8.9%)	859,388	(9.6%)
2 diseases	6,799,080	(7.6%)	631,794	(8.1%)	687,732	(9.0%)	933,542	(10.4%)
3 diseases	5,534,827	(6.2%)	510,570	(6.6%)	638,438	(8.3%)	881,741	(9.8%)
4 diseases	4,261,753	(4.8%)	382,265	(4.9%)	509,123	(6.7%)	729,058	(8.1%)
≥ 5 diseases	6,574,213	(7.4%)	489,921	(6.3%)	703,297	(9.2%)	1,106,284	(12.3%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		65-69		70-74	
	88,923,000	(100%)	9,155,000	(100%)	7,929,000	(100%)
Men	44,288,000	(49.8%)	4,414,000	(48.2%)	3,690,000	(46.5%)
AIDS/HIV	34,034	(0.0%)	3,793	(0.0%)	2,940	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	1,296,908	(14.2%)	1,323,445	(16.7%)
Cerebrovascular disease	5,773,295	(6.5%)	1,404,663	(15.3%)	1,836,456	(23.2%)
Chronic pulmonary disease	17,303,735	(19.5%)	2,445,425	(26.7%)	2,485,540	(31.3%)
Congestive heart failure	4,317,076	(4.9%)	931,107	(10.2%)	1,374,790	(17.3%)
Dementia	410,326	(0.5%)	83,286	(0.9%)	271,063	(3.4%)
Diabetes mellitus	12,689,040	(14.3%)	2,891,848	(31.6%)	3,029,762	(38.2%)
Hemiplegia or paraplegia	424,609	(0.5%)	81,998	(0.9%)	148,087	(1.9%)
Liver disease	11,341,444	(12.8%)	2,094,406	(22.9%)	2,092,035	(26.4%)
Metastatic solid tumor	1,235,336	(1.4%)	300,280	(3.3%)	292,970	(3.7%)
Myocardial infarction	769,977	(0.9%)	197,033	(2.2%)	213,037	(2.7%)
Peptic ulcer disease	11,238,524	(12.6%)	2,053,538	(22.4%)	2,165,800	(27.3%)
Peripheral vascular disease	5,197,644	(5.8%)	1,181,335	(12.9%)	1,432,557	(18.1%)
Renal disease	1,261,138	(1.4%)	257,988	(2.8%)	391,604	(4.9%)
Rheumatologic disease	1,928,685	(2.2%)	374,826	(4.1%)	372,134	(4.7%)
no disease	57,293,691	(64.4%)	3,803,485	(41.5%)	2,407,794	(30.4%)
1 disease	8,464,436	(9.5%)	785,842	(8.6%)	758,403	(9.6%)
2 diseases	6,799,080	(7.6%)	1,013,307	(11.1%)	908,900	(11.5%)
3 diseases	5,534,827	(6.2%)	1,074,487	(11.7%)	1,047,899	(13.2%)
4 diseases	4,261,753	(4.8%)	886,159	(9.7%)	923,584	(11.6%)
≥ 5 diseases	6,574,213	(7.4%)	1,591,721	(17.4%)	1,882,418	(23.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation and death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Overall[a]												
	Full Model			**20-39 years**			**40-59 years**			**60-71 years**		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	1.02	1.01	1.02									
Sex	0.97	0.95	0.99	0.36	0.34	0.37	1.29	1.25	1.33	1.44	1.38	1.51
≥2 diseases	2.17	2.12	2.21	2.17	2.05	2.29	2.31	2.24	2.38	2.05	1.97	2.14
Men[b]												
Age	1.03	1.03	1.04									
≥2 diseases	2.04	1.98	2.10	2.81	2.56	3.07	2.25	2.17	2.34	1.94	1.84	2.04
Women[b]												
Age	0.99	0.99	1.00									
≥2 diseases	2.22	2.15	2.30	1.91	1.78	2.04	2.42	2.30	2.54	2.28	2.12	2.44

[a]References are female for sex, no disease for morbidity variables

[b]Reference is no disease for morbidity variables

HR; hazard ratio, CI; confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig. 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl. Table 2
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1, Suppl. Tables 3-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, Fig. 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, Fig. 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063216.R1
Article Type:	Original research
Date Submitted by the Author:	02-Sep-2022
Complete List of Authors:	Saito, Yoshiyuki; The University of Tokyo, Department of Health Economics & Outcomes Research; Kyoto University School of Public Health, Department of Health Informatics Igarashi, Ataru ; The University of Tokyo, Department of Health Economics & Outcomes Research; Yokohama City University School of Medicine Graduate School of Medicine, Unit of Public Health and Preventive Medicine Nakayama, Takeo; Kyoto University School of Public Health, Department of Health Informatics Fukuma, Shingo; Kyoto University, Department of Human Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health economics, Health informatics, Health policy
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors

Yoshiyuki Saito[1,2*] PharmD, Ataru Igarashi[1,3] PhD, Takeo Nakayama[2] MD PhD, Shingo Fukuma[4] MD

Author Affiliations

[1]Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[2]Department of Health Informatics, School of Public Health, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

[3]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa 236-0027, Japan

[4]School of Human Health Sciences, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

Running head

The burden of multimorbidity in Japan 2014-2019

*Corresponding author

Yoshiyuki Saito, PharmD

Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

E-mail: saito.yoshiyuki.86x@kyoto-u.jp

Tel: +81-3-5841-4828

Word count: 3492 (incl. abstract)

Tables: 1

Figures: 3

Supplementary Tables: 4

Abstract

Objective

To describe the prevalence of multimorbidity and its associations with clinical outcomes across age groups.

Design

Retrospective cohort study using nationwide medical claims data.

Setting

Carried out in Japan between April 2014 and March 2019.

Participants

N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE) were included into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals were included into the cohort data set spanning FY2014-FY2018.

Exposures

Multimorbidity was defined as having ≥2 of 15 chronic conditions according to the ICD-10 codes of the Charlson Comorbidity Index.

Primary and Secondary Outcomes

Primary outcome: The standardised prevalence of multimorbidity across age groups was evaluated using data from FY 2014 and extrapolated to the Japanese total population. Secondary Outcome: Hospitalisation or death events were traced by month using medical claims data and insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation and/or death events across age groups were analysed using a Cox regression model.

Results

The standardised prevalence rate of multimorbidity in nationwide Japanese total population was approximately 5% (ages 25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%),), and 60% (70-74).

Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity had a higher incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41 [95% CI, 3.23-3.53] in ages ≥60). The difference in the incidence of clinical events between multimorbidity and no-multimorbidity was larger than that between age groups.

Conclusions

Multimorbidity is already prevalent in the middle-aged generation and is associated with poor clinical outcomes. These findings underscore the significance of multimorbidity and highlight the urgent need for preventive intervention at the public health care level.

Article Summary

Strengths and limitations of this study

- The current study covers a wide age range of individuals from a nationwide general population.
- Japan`s high medical insurance coverage rate made it possible to comprehensively identify chronic diseases from receipts.
- Longitudinal analysis enabled the examination of clinical outcomes of multiple co-morbidities.
- The prevalence of multimorbidity may be underestimated because the target population comprised regular employees and their families and might accordingly be healthier than the general population.

Keywords

chronic disease, insurance claims, middle age, multimorbidity, preventive medicine

Introduction

Aging societies worldwide face the problem of how to provide adequate and affordable health care for a growing number of patients with multiple chronic conditions, termed multimorbidity.[1,2] Managing multimorbidity is becoming a global challenge on the clinical and public healthcare level not only in high-, but also in low- and middle-income countries.[3] Many epidemiological studies on multimorbidity have shown its association with age, socio-demographic and socio-economic factors.[4-7] In addition, numerous studies have shown that multiple comorbidities are common in older people.[8-11] It has been reported that multimorbid older patients had more than twice as many contacts per year with physicians than those without multimorbidity[12] and that the likelihood of being hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.[8] On the other hand, the accumulation of chronic diseases occurs continuously from middle age. A number of recent studies conducted in various countries have reported that the onset of multimorbidity is shifting towards younger age groups.[6, 13-15] However, multimorbidity studies tend to focus on older people, and in-depth knowledge on multimorbidity in younger age groups is lacking.

Here, to evaluate the current status of multimorbidity across age groups and examine its association with clinical outcomes, we analysed a large nationwide medical claims

cohort. Our findings add to existing knowledge by showing that multimorbidity has a significant impact on health starting from middle age and underscore the need for preventive intervention on the public health care level.

Materials and Methods

Data source

We used the nationwide medical claims and enrolment data of the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE), which is one of the largest social insurance associations in Japan. HIA^{2}CE is a comprehensive insurer which includes 1700 companies, from small engineering companies to middle and large construction companies across Japan. This claims database covers a total of 400 000 insured persons, consisting of employees and their dependents.

Insured-based data base is used widely and one of the popular real-world data in Japan.[16] Japan has maintained a universal health coverage system since 1961. All medical information regarding clinical practice covered by this health insurance is included in the medical claims data, except for self-financed medical care and individuals who receive public assistance. Furthermore, medical facilities have been obliged since 2011 to submit medical claims data as an electronic record. Medical claims data include the names of the diagnosed diseases, the names of medical procedures, and the names of prescribed medications, among others. In the present study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and hospitalisations and deaths from the medical claims data in HIA^{2}CE from FY2014 to

FY2018 (April 2014 to March 2019). The enrolment data from HIA^{2}CE includes the medical characteristics and in-out information of insured persons as of April 2019.

Research design and study population

We prepared two data sets for analysis. The first was cross-sectional data set contained baseline data of FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The study population for this baseline data set included individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since HIA2CE is a type of insurance for workers in Japan, database include only under 75 years individuals. Therefore, maximum age in this cohort was 74 years. Participants younger than 20 in FY2014 as well as participants who died during FY2014 were excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to FY2018 (April 2014 to March 2019). Second data set contained participants insured in whole period. We used this cohort data set to conduct Cox regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).

Definition of diagnosed diseases and multimorbidity

There are a variety of definitions for chronic conditions in multimorbidity studies.[17-19] We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the diseases associated with a significant risk of clinical events.[20] The reason, we used CCI, was that we focused on describing the prevalence of each disease and also assessing the association of multimorbidity on hospitalisation or death. The CCI Canadian version has been reported to be applicable to Japanese claims data.[21] We therefore defined diagnosed diseases using medical claims data following ICD-10 codes of the CCI Canada version. We merged the conditions “diabetes with chronic complication” and “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease” and “moderate or severe liver disease” into “liver disease”. The following 15 chronic conditions were included: AIDS/HIV, any malignancy (including lymphoma and leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour, liver disease, myocardial infarction, peptic ulcer disease, renal disease, and rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in the Supplement. Multimorbidity status was defined as the concurrent presence of two or more (≥2) diagnosed diseases among these conditions.[22, 23] We only used confirmed diagnoses, not including suspected diagnoses, in Japanese claims data.

Definition of outcome events; hospitalisation or death

We defined two composite outcomes, hospitalisation or death, which occurred during the period from FY2015 to FY2018. Using the medical claims data, both events were traced by month. In Japan, the validity of death event information is reported to be less sensitive if derived from medical claims data only.[24, 25] Therefore, we also used death information from enrolment data recorded by the insurer: if either contained death information, this was defined as a death event.

Estimation of diagnosed disease prevalence to nationwide scale

Diagnosed disease prevalence from baseline data was standardised to the nationwide Japanese total population. We calculated prevalence rates according to groups by 5-year age brackets and sex. Then, we estimated the prevalence rates standardized to Japanese total population (age-sex standardized prevalence rate), using the number from the vital statistics 2014 in Japan.[26]

The association of multimorbidity with outcome by age group

To examine the association of multimorbidity with outcome by age group, we performed Cox regression analysis adjusted by sex using cohort data from four consecutive years (FY2015 to FY2018). The independent and additive effect of multimorbidity and aging, we defined combined categories according to three age groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥60, respectively) and the binary status of multimorbidity, with the reference set as no multimorbidity individuals aged 20-39. This model was able to show HR for aging alone (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-39 ages without multimorbidity).

Statistical analysis

Cox regression was conducted for the association of multimorbidity with outcome by age group. Results were considered statistically significant at a two-sided *P*-value of less than 0.05. All analyses were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX, USA).

Patient and Public involvement

Patients or the public were not involved in this research. However, the results of this study will be disseminated to the public through various means including published papers and presentations.

Results

Study participants

We analysed *n* = 246 671 individuals in the baseline data set in FY2014 (Table1) and *n* = 181 959 individuals in the cohort data set FY2014-FY2018. Because follow-up was four years, the cohort data set was slightly smaller than the baseline data set, especially as a number of young individuals aged 20-24 and older individuals aged >60 dropped out. This may be due to raising children or early retirement, and explains the higher proportion of men in the cohort data set. Mean age and co-morbidity numbers among CCI diseases were mostly comparable between the two data sets, although the prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in disease prevalence between genders were observed. Notably, men had a higher prevalence of diabetes mellitus (*P* = 0.001) whereas women had a higher prevalence of chronic pulmonary disease (*P* = 0.002).

Estimated prevalence of multimorbidity in the Japanese total population

The prevalence of diagnosed diseases in FY2014 was applied to the vital statistics of the Japanese population in 2014. The standardised prevalence of multimorbidity was

estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population (eTable 3A in the Supplement). The prevalence rate of multimorbidity increased with age, i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of diseases as well as below results are shown in eTable 3B in the Supplement). Figure 2B shows the types of disease and their prevalence across age groups. The top five diseases across the age groups “young” (20-39), “middle-age (40-59), and “old” (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, and any malignancy; “middle-age”: chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-44, the top five accelerating diseases were dementia, cerebrovascular disease, peripheral vascular disease, metastatic tumour, and congestive heart failure.

The association of multimorbidity with outcome by age group.

Cox regression analysis showed that young individuals aged 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages ≥60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with multimorbidity has a risk more than ages ≥60 without multimorbidity.

We also assessed HRs for non-multimorbid and multimorbid women and men separately and found that women had a lower HR than men in the 20-39 age group but a higher HR than men in the ≥60 age group (eTable 4 in the Supplement).

Discussion

In this study we analysed nationwide medical claims data for 15 chronic diseases in a large cohort of the general population of Japan. As key findings, standardised prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for women. Further, age group-specific prevalence rates for multimorbidity ranged from 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an accelerating increase after age 40. Importantly, significant differences in the clinical outcomes of multimorbidity versus no multimorbidity were already present in young and middle-aged individuals.

The present study drew individuals covering a wide age range from a nationwide general population. This allowed us to examine the burden of multiple co-morbidities in young, middle-aged and old age groups in the real world. In addition, because Japan has a high medical insurance coverage rate, it was possible to comprehensively identify chronic diseases from receipts. Further, longitudinal analysis enabled us to examine the clinical outcomes of multiple co-morbidities. With regard to limitations, the target population comprised regular employees and their families and might accordingly be healthier than the general population. Also, we defined multimorbidity by disease list included in CCI most likely to lead to death, hence, we were not able to consider other

diseases associated with health-related quality of life loss. The presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in individuals already suffering from other chronic diseases,[27] younger people,[28] and people with a low socio-economic status. [29] Such diseases often remain undiagnosed or underreported in health records. [30] These limitations likely contributed to an underestimation of multimorbidity in our cohort. Further, because we did not manually verify the presence of disease using the physician's medical records data or medication information, disease names extracted from the medical claims data might be incorrect in some cases. In particular, Japanese physicians sometimes change the name of the disease in the medical record to the "correct" disease name for the medication they wish to prescribe, a practice called "disease name for claims data".

Because of differences in data sources and study populations, direct comparison of population-based prevalence rates between studies is not straightforward. Nonetheless, the standardised prevalence rates for multimorbidity as reported in the present study - 26.1% for men and 26.0% for women - are similar to those reported by recent studies in other high-income countries, such as the United States (25% in men, 25% in women), [31] England (24.4% in men, 30% in women), [32] Canada (24.3% whole population),[5] and Denmark (19.3% in men, 23.7% in women).[6] Also recently some Asian countries

reported similar prevalence, Iran (13.4% in men, 25.0% in women),[33] India, Bangladesh (53.7% - 56.5% in both gender, over aged 60).[34] Many previous studies on multimorbidity focused on the older generation, aged 65 and up, because of the larger number of chronic diseases in this age group and the increasing number of people entering it. However, our present data show that already approximately 10% of 30-34-, 19% of 45-49-, and 33% of 55-59-year-olds have ≥2 chronic diseases. Further, 1% of 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥5 chronic diseases. These results show that multimorbidity is already prominent in the middle-aged population. Recent studies reported similar or slightly higher prevalence rates for ≥2 chronic diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)[29] and a Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)[5] population, although these two studies also included mental diseases and osteoporosis, which our present study did not. Our present study shows that, among 15 chronic diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes mellitus, prevalence in the present study is similar to that previously reported in an American population (15-30% in individuals aged 55-65)[29] but higher than that in a

Canadian population (16.6% in individuals aged 55-64)[4]. The prevalence of chronic pulmonary disease in our present 55-65-year-olds was almost twice as high as those seen for the combined prevalence of asthma and chronic obstructive pulmonary disease (COPD) in an American population aged 55-65 years (5% for men and 10% for women)[29] and in a Canadian population aged 55-64 years (13.7%).[5] This difference might have arisen due to our inclusion of various other pulmonary diseases besides asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in the present study was comparable to that seen in an adult population in Northern Italy[35] and in an adult population in Korea,[36] although this comparison requires care since the types of liver disease in these studies and the age groups included vary.

Analysis of clinical outcomes using Cox regression revealed that the presence of multimorbidity increased HRs in all age groups, including young individuals. In addition, comparison of the increased HRs resulting from multimorbidity versus no multimorbidity showed that the impact of multimorbidity exceeds that of increasing age. These results indicate that multimorbidity places a burden on all age groups.

Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and any malignancy) in the present study are lifestyle-related diseases that develop slowly over time. This trend should be

greeted with alarm. We trust that this study raises awareness of the potential health risks and burden associated with the early onset of multimorbidity in young and middle-age, the period when one is busy working and raising children. Future studies should investigate the specific lifestyle factors associated with an elevated risk of multimorbidity in the Japanese working population. Ultimately, public health care policies should be aimed at efforts to reverse the trend toward early multimorbidity onset.

In conclusion, the present study revealed that the impact of multimorbidity is already prominent in middle-aged Japanese, with elevated adverse events such as hospitalisation or death. In addition, the risk posed by multimorbidity exceeds that of aging in all age groups. These results underscore the need to undertake healthcare intervention against the onset of multimorbidity before middle-age, and not to leave it as a problem for geriatricians.

Ethical Approval

The present study was approved by the Institutional Review Board (IRB) of Kyoto University (approval number: R0817). All data were anonymised before analysis and none of the researchers had access to patient-identifiable information. The IRB waived informed consent for this observational study.

Data Availability Statement

All data are incorporated into the article and its online supplementary material.

Author Contributions

Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS. Administrative, technical, or material support: YS, SF. Study supervision: SF, AI, TN. YS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval and agreed to be accountable for all aspects of work.

Acknowledgements

The authors are grateful to HIA^{2}CE for providing data for the present study.

Funding

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in the design of the study; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Competing Interests

None declared.

Patient Consent for Publication

Not applicable.

Figure Legends

Figure 1. Participant selection flowchart. FY; fiscal year

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A**) Percentage of the population having 0 to ≥5 chronic diseases by age group. **B**)

Prevalence of the top ten chronic diseases by age group. **C**) The top ten chronic diseases with the steepest increase after age 40-44 years.

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

References

1 Bleich SN, Sherrod C, Chiang A*, et al*. Systematic Review of Programs Treating High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities in the United States, 2008-2014. *Prev Chronic Dis*. Nov 12 2015;12:E197. doi:10.5888/pcd12.150275

2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. *Prev Med Rep*. Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008

3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y, Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614. doi:10.1371/journal.pone.0243614

4 Low LL, Kwan YH, Ko MSM*, et al*. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging

Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245. doi:10.1001/jamanetworkopen.2019.15245

5 Pefoyo AJ, Bronskill SE, Gruneir A*, et al*. The increasing burden and complexity of multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-1733-2

6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8

7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of multimorbidity on healthcare utilisation and work productivity by socioeconomic groups: Cross-sectional analyses of Australia and Japan. *PLoS One*. 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281

8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. *BMC Health Serv Res*. Jan 22 2015;15:23. doi:10.1186/s12913-015-0698-2

9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-sectional study based on nationwide claims data. *BMJ Open*. Jun 9 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333

10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on

administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812. doi:10.1136/bmjopen-2016-012812

11 Picco L, Achilla E, Abdin E*, et al*. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10 2016;16:173. doi:10.1186/s12913-016-1421-7

12 van den Bussche H, Schon G, Kolonko T*, et al*. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54

13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152. doi:10.1186/s12916-017-0913-6

14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising burden of multimorbidity and related socio-demographic factors: a repeated cross-sectional study of Ontarians. *Can J Public Health*. Apr 13 2021;doi:10.17269/s41997-021-00474-y

15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England, 2002-2015. *J Comorb*. Jan-Dec 2019;9:2235042X19872030. doi:10.1177/2235042X19872030

16 Katsutoshi H, Annabel B, Yasuhiko M, et al. Current Status, Challenges, and Future Perspectives of Real-World Data and Real-World Evidence in Japan.

Drugs - Real World Outcomes. 2021;8:459–480. doi:org/10.1007/s40801-021-00266-3

17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments used for measuring the association of the level of multimorbidity and clinically important outcomes. *BMJ Open*. 2021;May 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.

18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.

19 Mikk J, Heti P, Anneli U, et al. Prevalence of chronic conditions and multimorbidity in Estonia: a population-based cross-sectional study. *BMJ Open.* 2021;Oct 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.

20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan H, Li B, Couris CM*, et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*. 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.

22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*. Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098

23 Le Reste JY, Nabbe P, Manceau B*, et al*. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001

24 Ooba N, Setoguchi S, Ando T*, et al*. Claims-based definition of death in Japanese claims database: validity and implications. *PLoS One*. 2013;8(5):e66116. doi:10.1371/journal.pone.0066116

25 Sakai M, Ohtera S, Iwao T*, et al*. Validation of claims data to identify death among aged persons utilizing enrollment data from health insurance unions. *Environ Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3

26 Statistics Bureau of Japan. Preliminary count of the Japanese population. Accessed March, 2014. http://www.stat.go.jp/data/jinsui/index.html

27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234

28 Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002

29 Rocca WA, Boyd CM, Grossardt BR, *et al*. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49. doi:10.1016/j.mayocp.2014.07.010

30 Cassell A, Edwards D, Harshfield A, *et al*. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. Apr 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465

31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al*. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251

32 St Sauver JL, Boyd CM, Grossardt BR, *et al*. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413

33 Masoomeh A, Azam M, Mehdi Y. et al. Multimorbidity as an important issue among women: results of a gender difference investigation in a large population-based cross-sectional study in West Asia. *BMJ Open*. 2017;May 9;7(5):e013548. doi: 10.1136/bmjopen-2016-013548.

34 Sanghamitra P, Subhashisa S, Mohammad AH, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review bmj open. *BMJ Open*. 2015 Oct 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.

35 Bellentani S, Tiribelli C, Saccoccio G*, et al*. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec 1994;20(6):1442-9. doi:10.1002/hep.1840200611

36 Park SH, Plank LD, Suk KT*, et al*. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr 2020;26(2):209-215. doi:10.3350/cmh.2019.0065

Supplementary Information

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population

	Baseline data in FY2014					
	Overall		**Men**		**Women**	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%
Men	144,237	58.5	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8
20-24	18,524	7.5	11,315	7.8	7,209	7.0
25-29	17,251	7.0	12,014	8.3	5,237	5.1
30-34	18,093	7.3	11,104	7.7	6,989	6.8
35-39	23,878	9.7	13,278	9.2	10,600	0.3
40-44	39,721	16.1	21,640	15.0	18,081	17.7
45-49	40,908	16.6	24,191	16.8	16,717	16.3
50-54	29,466	11.9	17,577	12.2	11,889	11.6
55-59	20,149	8.2	11,343	7.9	8,806	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4
65-69	11,931	4.8	6,768	4.7	5,163	5.0
70-74	5,472	2.2	2,301	1.6	3,171	3.1
AIDS/HIV	96	0.0	62	0.0	34	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9
Dementia	447	0.2	210	0.1	237	0.2
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6
Renal disease	2,573	1.0	1,751	1.2	822	0.8
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3
Disease no. among CCI						
no disease	171,140	69.4	101,857	70.6	69,283	67.6
1 disease	22,947	9.3	12,032	8.3	10,915	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7
Multimorbidity (≥2 diseases among CCI)	52,584	21.3	30,348	21.0	22,236	21.7

Values are numbers (%) unless otherwise stated.
[a] Any malignancy includes leukemia and lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

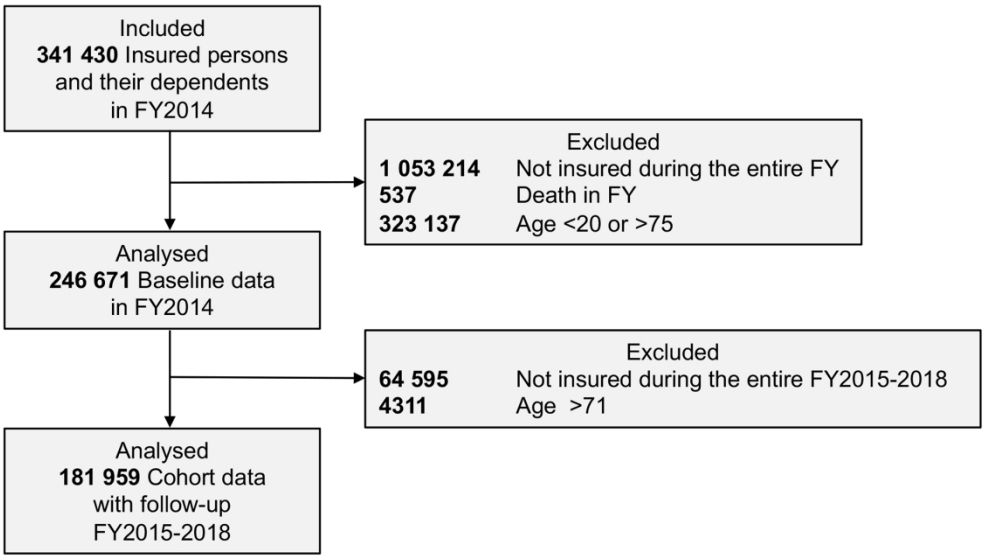

Figure 1. Participant selection flowchart. FY; fiscal year

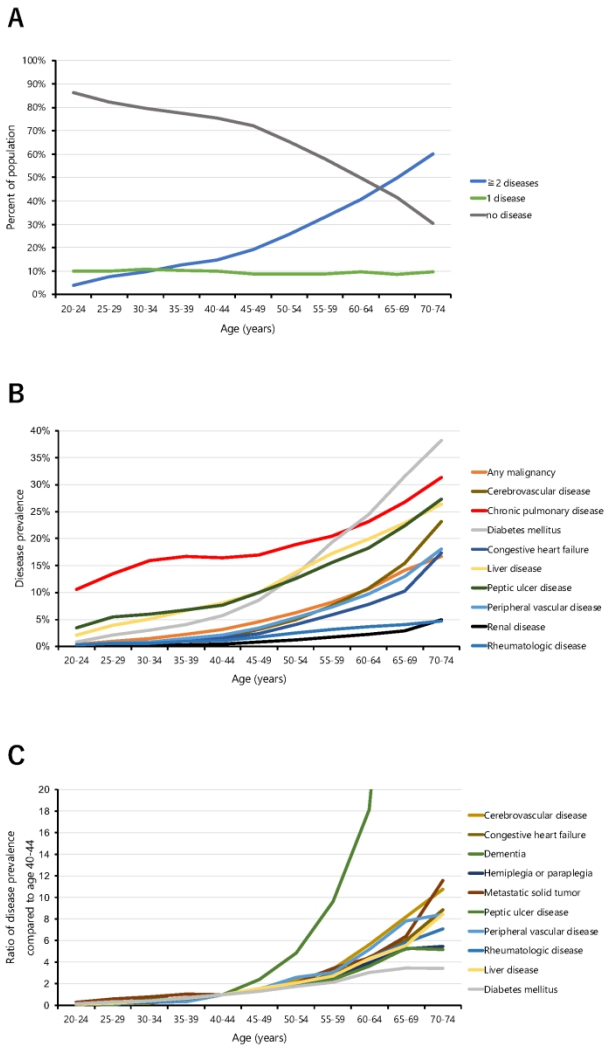

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥5 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44 years.

297x420mm (200 x 200 DPI)

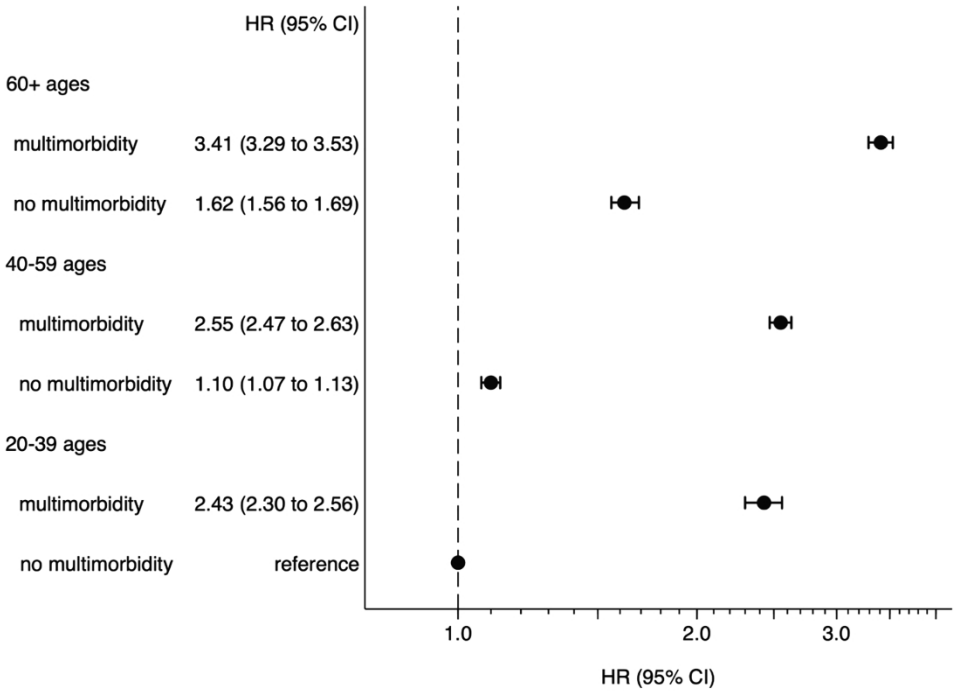

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

Supplementary material

Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Diseases	ICD-10 codes
AIDS/HIV	B20.x-B22.x, B24.x
Any malignancy, incl. leukemia and lymphoma	C00.x-C26.x, C30.x-C34.x, C37.x-C41x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.3, C88.7, C88.9, C90.0, C90.1, C91.x- C93.x, C94.0-C94.3, C94.5, C94.7, C95.x, C96.x, C43.x, C88.0-C88.2, C90.2, C94.4, C97.x
Cerebrovascular disease	I69.x, G45.x, G46.x, H34.0, I60.x-I68.x
Chronic pulmonary disease	J41.x-J47.x, J60.x-J66.x, I27.8, I27.9, J40.x, J67.x, J68.4, J70.1, J70.3
Congestive heart failure	I50.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5- I42.9, I43.x, P29.0
Dementia	F00.x-F02.x, F03.x, F05.1, G30.x, G31.1
Diabetes with chronic complication	E10.2-E10.4, E11.2-E11.4, E13.2-E13.4, E14.2-E14.4, E10.5, E10.7, E11.5, E11.7, E12.2-E12.5, E12.7, E13.5, E13.7, E14.5, E14.7
Diabetes without chronic complication	E10.1, E10.9, E11.1, E11.9, E13.1, E13.9, E14.1, E14.9, E10.0, E10.6, E10.8, E11.0, E11.6, E11.8, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.6, E13.8, E14.0, E14.6, E14.8
Hemiplegia or paraplegia	G81.x, G82.0-G82.2, G04.1, G11.4, G80.1, G80.2, G82.3-G82.5, G83.0-G83.4, G83.9
Metastatic solid tumor	C77.x-C79.x, C80.x
Mild liver disease	K70.3, K71.7, K73.x, K74.3- K74.6, B18.x, K70.0-K70.2, K70.9, K71.3-K71.5, K74.0-K74.2, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	K72.1, K72.9, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K76.5
Myocardial infarction	I25.2, I21.x, I22.x
Peptic ulcer disease	K25.4-K25.7, K26.4-K26.7, K27.4-K27.7, K28.4-K28.7, K25.0-K25.3, K25.9, K26.0-K26.3, K26.9, K27.0-K27.3, K27.9, K28.0-K28.3, K28.9
Peripheral vascular disease	I71.x, I73.9, Z95.8, Z95.9, I70.x, I73.1, I73.8, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9

Renal disease	N18.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Rheumatology disease	M05.x, M06.0, M32.x, M33.2, M34.x, M35.3, M06.1-M06.4, M06.8, M06.9, M31.5, M33.0, M33.1, M33.9, M35.1, M36.0

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

	Baseline data in FY2014		Cohort data		*P*-value[c]
N	242,360	(100%)	181,959	(100%)	
Men	142,471	(58.8%)	111,088	(61.1%)	<0.01
Age (Mean, SD)	44.5	(12.5)	44.7	(10.6)	<0.01
20-24	18,524	(7.6%)	5,052	(2.8%)	<0.01
25-29	17,251	(7.1%)	12,675	(7.0%)	
30-34	18,093	(7.5%)	14,784	(8.1%)	
35-39	23,878	(9.9%)	20,508	(11.3%)	
40-44	39,721	(16.4%)	35,168	(19.3%)	
45-49	40,908	(16.9%)	37,124	(20.4%)	
50-54	29,466	(12.2%)	25,906	(14.2%)	
55-59	20,149	(8.3%)	13,052	(7.2%)	
60-64	21,278	(8.8%)	10,735	(5.9%)	
65-69	11,931	(4.9%)	6,246	(3.4%)	
70-71	1,161	(0.5%)	709	(0.4%)	
AIDS/HIV	94	(0.0%)	74	(0.0%)	0.76
Any malignancy[a]	11,343	(4.7%)	8,377	(4.6%)	0.24
Cerebrovascular disease	9,860	(4.1%)	6,971	(3.8%)	<0.01
Chronic pulmonary disease	41,866	(17.3%)	32,093	(17.6%)	<0.01
Congestive heart failure	7,751	(3.2%)	5,710	(3.1%)	0.27
Dementia	291	(0.1%)	190	(0.1%)	0.13
Diabetes mellitus	25,716	(10.6%)	18,755	(10.3%)	<0.01
Hemiplegia or paraplegia	729	(0.3%)	507	(0.3%)	0.19

Liver disease	25,999	(10.7%)	19,725	(10.8%)	0.24
Metastatic solid tumor	2,381	(1.0%)	1,823	(1.0%)	0.53
Myocardial infarction	1,526	(0.6%)	1,092	(0.6%)	0.22
Peptic ulcer disease	24,859	(10.3%)	18,594	(10.2%)	0.68
Peripheral vascular disease	9,623	(4.0%)	7,083	(3.9%)	0.20
	Baseline data in FY2014		**Cohort data**		***P*-value[c]**
N	242,360	(100%)	181,959	(100%)	
Renal disease	2,350	(1.0%)	1,747	(1.0%)	0.75
Rheumatologic disease	3,931	(1.6%)	2,926	(1.6%)	0.72
At least one disease among the top five[b]	69,014	(28.5%)	50,660	(27.8%)	<0.01
Disease no. among CCI (Mean, SD)	0.8	(1.6)	0.8	(1.6)	0.16
0 disease	169,872	(70.1%)	129,037	(70.9%)	<0.01
1 disease	22,514	(9.3%)	15,532	(8.5%)	
2 diseases	16,605	(6.9%)	12,375	(6.8%)	
3 diseases	12,242	(5.1%)	9,046	(5.0%)	
4 diseases	9,076	(3.7%)	6,816	(3.7%)	
≥ 5 diseases	12,051	(5.0%)	9,153	(5.0%)	
Multimorbidity (≥2 diseases among CCI)	49,974	(20.6%)	37,390	(20.5%)	
Composite outcomes	36,893	(15.2%)	31,224	(17.2%)	<0.01
Death	1,507	(0.6%)	1,507	(0.8%)	
Hospitalisation	36,495	(15.1%)	30,826	(16.9%)	

[a] Any malignancy includes leukemia and lymphoma.

[b] Top 5 diseases include chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and cerebrovascular disease.

SD; standard deviation, CCI; Charlson Comorbidity Index
[c] Age (Mean) and Co-morbidity no. (Mean): Student`s t-test. All other variables: Pearson's chi-square test.

Supplementary eTable 3A. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population by gender

	Baseline data in FY2014						Japanese total population					
	Overall		Men		Women		Overall		Men		Women	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%	*N*=88,923,000	%	*N*=44,288,000	%	*N*=44,640,000	%
Men	144,237	58.5	-	-	-	-	44,288,000	49.8	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8	48.0	15.3	47.7	15.3	48.4	15.4
20-24	18,524	7.5	11,315	7.8	7,209	7.0	6,203,000	7.0	3,192,000	7.2	3,012,000	6.7
25-29	17,251	7.0	12,014	8.3	5,237	5.1	6,677,000	7.5	3,414,000	7.7	3,264,000	7.3
30-34	18,093	7.3	11,104	7.7	6,989	6.8	7,466,000	8.4	3,788,000	8.6	3,680,000	8.2
35-39	23,878	9.7	13,278	9.2	10,600	0.3	8,670,000	9.8	4,394,000	9.9	4,276,000	9.6
40-44	39,721	16.1	21,640	15.0	18,081	17.7	9,793,000	11.0	4,956,000	11.2	4,837,000	10.8
45-49	40,908	16.6	24,191	16.8	16,717	16.3	8,609,000	9.7	4,329,000	9.8	4,278,000	9.6
50-54	29,466	11.9	17,577	12.2	11,889	11.6	7,790,000	8.8	3,903,000	8.8	3,887,000	8.7
55-59	20,149	8.2	11,343	7.9	8,806	8.6	7,653,000	8.6	3,802,000	8.6	3,853,000	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4	8,979,000	0.1	4,406,000	9.9	4,573,000	10.2
65-69	11,931	4.8	6,768	4.7	5,163	5.0	9,155,000	10.3	4,414,000	10.0	4,741,000	10.6
70-74	5,472	2.2	2,301	1.6	3,171	3.1	7,928,000	8.9	3,690,000	8.3	4,239,000	9.5
AIDS/ HIV	96	0.0	62	0.0	34	0.0	34,034	0.0	18,979	0.0	15,055	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3	5,775,260	6.5	2,668,349	6.0	3,106,911	7.0
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3	5,773,295	6.5	3,023,765	6.8	2,749,530	6.2
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2	17,303,735	19.5	7,713,864	17.4	9,589,871	21.5
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9	4,317,076	4.9	2,459,170	5.6	1,857,906	4.2
Deme ntia	447	0.2	210	0.1	237	0.2	410,326	0.5	179,350	0.4	230,976	0.5
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2	12,689,040	14.3	7,122,240	16.1	5,566,801	12.5
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3	424,609	0.5	253,040	0.6	171,569	0.4
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9	11,341,444	2.8	6,031,029	13.6	5,310,415	11.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2	1,235,336	1.4	598,734	1.4	636,601	1.4
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3	769,977	0.9	575,894	1.3	194,083	0.4
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3	11,238,524	12.6	5,485,994	12.4	5,752,530	12.9
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6	5,197,644	5.8	2,503,359	5.7	2,694,285	6.0
Renal disease	2,573	1.0	1,751	1.2	822	0.8	1,261,138	1.4	784,770	1.8	476,367	1.1
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7	1,928,685	2.2	530,072	1.2	1,398,613	3.1
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3	30,041,150	33.8	14,676,045	33.1	15,365,106	34.4
Disease no. among CCI												
no disease	171,140	69.4	101,857	70.6	69,283	67.6	57,293,691	64.4	29,006,814	65.5	28,286,877	63.4
1 disease	22,947	9.3	12,032	8.3	10,915	10.7	8,464,436	9.5	3,702,220	8.4	4,762,216	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9	6,799,080	7.6	3,029,535	6.8	3,769,544	8.4
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4	5,534,827	6.2	2,652,231	6.0	2,882,596	6.5
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6	4,261,753	4.8	2,242,062	5.1	2,019,691	4.5
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7	6,574,213	7.4	3,655,138	8.3	2,919,075	6.5
Multimorbidity	52,584	21.3	30,348	21.0	22,236	21.7	23,169,873	26.1	11,578,966	26.1	11,590,906	26.0

(≥2 diseases among CCI)

Values are numbers (%) unless otherwise

[a] Any malignancy includes leukemia and lymphoma.

FY; fiscal year

SD; standard deviation

CCI; Charlson Comorbidity Index

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		20-24		25-29		30-34	
	88,923,000	(100%)	6,204,000	(100%)	6,678,000	(100%)	7,468,000	(100%)
Men	44,288,000	(49.8%)	3,192,000	(51.5%)	3,414,000	(51.1%)	3,788,000	(50.7%)
AIDS/HIV	34,034	(0.0%)	1,400	(0.0%)	1,137	(0.0%)	1,394	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	24,047	(0.4%)	60,604	(0.9%)	103,907	(1.4%)
Cerebrovascular disease	5,773,295	(6.5%)	12,484	(0.2%)	23,767	(0.4%)	40,440	(0.5%)
Chronic pulmonary disease	17,303,735	(19.5%)	656,012	(10.6%)	901,156	(13.5%)	1,184,702	(15.9%)
Congestive heart failure	4,317,076	(4.9%)	21,322	(0.3%)	34,950	(0.5%)	52,469	(0.7%)
Dementia	410,326	(0.5%)	418	(0.0%)	0	(0.0%)	1,053	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	50,290	(0.8%)	141,852	(2.1%)	228,348	(3.1%)
Hemiplegia or paraplegia	424,609	(0.5%)	3,782	(0.1%)	7,489	(0.1%)	10,227	(0.1%)
Liver disease	11,341,444	(12.8%)	129,091	(2.1%)	259,190	(3.9%)	380,993	(5.1%)
Metastatic solid tumor	1,235,336	(1.4%)	6,706	(0.1%)	9,643	(0.1%)	15,804	(0.2%)
Myocardial infarction	769,977	(0.9%)	3,510	(0.1%)	3,859	(0.1%)	7,438	(0.1%)
Peptic ulcer disease	11,238,524	(12.6%)	213,860	(3.4%)	364,164	(5.5%)	444,445	(6.0%)
Peripheral vascular disease	5,197,644	(5.8%)	20,276	(0.3%)	42,759	(0.6%)	60,055	(0.8%)
Renal disease	1,261,138	(1.4%)	6,164	(0.1%)	11,118	(0.2%)	19,957	(0.3%)
Rheumatologic disease	1,928,685	(2.2%)	17,602	(0.3%)	35,051	(0.5%)	43,777	(0.6%)
no disease	57,293,691	(64.4%)	5,352,990	(86.3%)	5,500,039	(82.4%)	5,935,225	(79.5%)
1 disease	8,464,436	(9.5%)	609,768	(9.8%)	666,087	(10.0%)	805,022	(10.8%)
2 diseases	6,799,080	(7.6%)	163,269	(2.6%)	310,407	(4.6%)	399,222	(5.3%)
3 diseases	5,534,827	(6.2%)	45,066	(0.7%)	104,758	(1.6%)	178,423	(2.4%)
4 diseases	4,261,753	(4.8%)	19,190	(0.3%)	52,301	(0.8%)	77,876	(1.0%)
≥ 5 diseases	6,574,213	(7.4%)	13,716	(0.2%)	44,409	(0.7%)	72,233	(1.0%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	241,241	(3.9%)	511,875	(7.7%)	727,754	(9.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		35-39		40-44		45-49	
	88,923,000	(100%)	8,670,000	(100%)	9,793,000	(100%)	8,607,000	(100%)
Men	44,288,000	(49.8%)	4,394,000	(50.7%)	4,956,000	(50.6%)	4,329,000	(50.3%)
AIDS/HIV	34,034	(0.0%)	4,592	(0.1%)	4,124	(0.0%)	3,069	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	198,069	(2.3%)	308,591	(3.2%)	393,299	(4.6%)
Cerebrovascular disease	5,773,295	(6.5%)	93,413	(1.1%)	170,645	(1.7%)	265,098	(3.1%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,446,109	(16.7%)	1,613,639	(16.5%)	1,462,084	(17.0%)
Congestive heart failure	4,317,076	(4.9%)	90,394	(1.0%)	155,193	(1.6%)	201,862	(2.3%)
Dementia	410,326	(0.5%)	734	(0.0%)	1,490	(0.0%)	3,606	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	352,333	(4.1%)	553,455	(5.7%)	737,731	(8.6%)
Hemiplegia or paraplegia	424,609	(0.5%)	13,621	(0.2%)	12,793	(0.1%)	19,669	(0.2%)
Liver disease	11,341,444	(12.8%)	577,316	(6.7%)	784,095	(8.0%)	858,769	(10.0%)
Metastatic solid tumor	1,235,336	(1.4%)	29,912	(0.3%)	56,656	(0.6%)	78,055	(0.9%)
Myocardial infarction	769,977	(0.9%)	8,925	(0.1%)	25,198	(0.3%)	37,793	(0.4%)
Peptic ulcer disease	11,238,524	(12.6%)	589,633	(6.8%)	749,581	(7.7%)	856,494	(10.0%)
Peripheral vascular disease	5,197,644	(5.8%)	127,339	(1.5%)	201,866	(2.1%)	288,167	(3.3%)
Renal disease	1,261,138	(1.4%)	30,634	(0.4%)	46,209	(0.5%)	73,397	(0.9%)
Rheumatologic disease	1,928,685	(2.2%)	79,300	(0.9%)	108,081	(1.1%)	143,756	(1.7%)
no disease	57,293,691	(64.4%)	6,707,086	(77.4%)	7,389,249	(75.5%)	6,205,507	(72.1%)
1 disease	8,464,436	(9.5%)	879,686	(10.1%)	969,263	(9.9%)	762,446	(8.9%)
2 diseases	6,799,080	(7.6%)	529,075	(6.1%)	633,182	(6.5%)	588,650	(6.8%)
3 diseases	5,534,827	(6.2%)	284,566	(3.3%)	352,334	(3.6%)	416,546	(4.8%)
4 diseases	4,261,753	(4.8%)	152,965	(1.8%)	232,087	(2.4%)	297,143	(3.5%)
≥ 5 diseases	6,574,213	(7.4%)	116,621	(1.3%)	216,885	(2.2%)	336,707	(3.9%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	1,083,227	(12.5%)	1,434,488	(14.6%)	1,639,046	(19.0%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		50-54		55-59		60-64	
	88,923,000	(100%)	7,790,000	(100%)	7,655,000	(100%)	8,979,000	(100%)
Men	44,288,000	(49.8%)	3,903,000	(50.1%)	3,802,000	(49.7%)	4,406,000	(49.1%)
AIDS/HIV	34,034	(0.0%)	2,979	(0.0%)	3,324	(0.0%)	5,281	(0.1%)
Any malignancy[a]	5,775,260	(6.5%)	483,592	(6.2%)	624,101	(8.2%)	958,696	(10.7%)
Cerebrovascular disease	5,773,295	(6.5%)	387,663	(5.0%)	573,513	(7.5%)	965,151	(10.7%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,469,169	(18.9%)	1,565,078	(20.4%)	2,074,822	(23.1%)
Congestive heart failure	4,317,076	(4.9%)	316,491	(4.1%)	443,956	(5.8%)	694,542	(7.7%)
Dementia	410,326	(0.5%)	7,254	(0.1%)	14,375	(0.2%)	27,048	(0.3%)
Diabetes mellitus	12,689,040	(14.3%)	1,028,899	(13.2%)	1,477,049	(19.3%)	2,197,472	(24.5%)
Hemiplegia or paraplegia	424,609	(0.5%)	26,826	(0.3%)	43,702	(0.6%)	56,416	(0.6%)
Liver disease	11,341,444	(12.8%)	1,063,948	(13.7%)	1,316,086	(17.2%)	1,785,515	(19.9%)
Metastatic solid tumor	1,235,336	(1.4%)	104,654	(1.3%)	136,279	(1.8%)	204,377	(2.3%)
Myocardial infarction	769,977	(0.9%)	65,457	(0.8%)	76,970	(1.0%)	130,757	(1.5%)
Peptic ulcer disease	11,238,524	(12.6%)	977,192	(12.5%)	1,190,533	(15.6%)	1,633,285	(18.2%)
Peripheral vascular disease	5,197,644	(5.8%)	411,839	(5.3%)	554,776	(7.2%)	876,673	(9.8%)
Renal disease	1,261,138	(1.4%)	95,578	(1.2%)	126,432	(1.7%)	202,057	(2.3%)
Rheumatologic disease	1,928,685	(2.2%)	191,910	(2.5%)	235,332	(3.1%)	326,918	(3.6%)
no disease	57,293,691	(64.4%)	5,087,646	(65.3%)	4,435,684	(57.9%)	4,468,987	(49.8%)
1 disease	8,464,436	(9.5%)	687,805	(8.8%)	680,727	(8.9%)	859,388	(9.6%)
2 diseases	6,799,080	(7.6%)	631,794	(8.1%)	687,732	(9.0%)	933,542	(10.4%)
3 diseases	5,534,827	(6.2%)	510,570	(6.6%)	638,438	(8.3%)	881,741	(9.8%)
4 diseases	4,261,753	(4.8%)	382,265	(4.9%)	509,123	(6.7%)	729,058	(8.1%)
≥ 5 diseases	6,574,213	(7.4%)	489,921	(6.3%)	703,297	(9.2%)	1,106,284	(12.3%)

Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	2,014,550	(25.9%)	2,538,590	(33.2%)	3,650,625	(40.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		65-69		70-74	
	88,923,000	(100%)	9,155,000	(100%)	7,929,000	(100%)
Men	44,288,000	(49.8%)	4,414,000	(48.2%)	3,690,000	(46.5%)
AIDS/HIV	34,034	(0.0%)	3,793	(0.0%)	2,940	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	1,296,908	(14.2%)	1,323,445	(16.7%)
Cerebrovascular disease	5,773,295	(6.5%)	1,404,663	(15.3%)	1,836,456	(23.2%)
Chronic pulmonary disease	17,303,735	(19.5%)	2,445,425	(26.7%)	2,485,540	(31.3%)
Congestive heart failure	4,317,076	(4.9%)	931,107	(10.2%)	1,374,790	(17.3%)
Dementia	410,326	(0.5%)	83,286	(0.9%)	271,063	(3.4%)
Diabetes mellitus	12,689,040	(14.3%)	2,891,848	(31.6%)	3,029,762	(38.2%)
Hemiplegia or paraplegia	424,609	(0.5%)	81,998	(0.9%)	148,087	(1.9%)
Liver disease	11,341,444	(12.8%)	2,094,406	(22.9%)	2,092,035	(26.4%)
Metastatic solid tumor	1,235,336	(1.4%)	300,280	(3.3%)	292,970	(3.7%)
Myocardial infarction	769,977	(0.9%)	197,033	(2.2%)	213,037	(2.7%)
Peptic ulcer disease	11,238,524	(12.6%)	2,053,538	(22.4%)	2,165,800	(27.3%)
Peripheral vascular disease	5,197,644	(5.8%)	1,181,335	(12.9%)	1,432,557	(18.1%)
Renal disease	1,261,138	(1.4%)	257,988	(2.8%)	391,604	(4.9%)
Rheumatologic disease	1,928,685	(2.2%)	374,826	(4.1%)	372,134	(4.7%)
no disease	57,293,691	(64.4%)	3,803,485	(41.5%)	2,407,794	(30.4%)
1 disease	8,464,436	(9.5%)	785,842	(8.6%)	758,403	(9.6%)
2 diseases	6,799,080	(7.6%)	1,013,307	(11.1%)	908,900	(11.5%)
3 diseases	5,534,827	(6.2%)	1,074,487	(11.7%)	1,047,899	(13.2%)
4 diseases	4,261,753	(4.8%)	886,159	(9.7%)	923,584	(11.6%)

≥ 5 diseases	6,574,213	(7.4%)	1,591,721	(17.4%)	1,882,418	(23.7%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	4,565,674	(49.9%)	4,762,801	(60.1%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Overall[a]												
	Full Model			**20-39 years**			**40-59 years**			**60-71 years**		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	1.02	1.01	1.02									
Sex	0.97	0.95	0.99	0.36	0.34	0.37	1.29	1.25	1.33	1.44	1.38	1.51
≥2 diseases	2.17	2.12	2.21	2.17	2.05	2.29	2.31	2.24	2.38	2.05	1.97	2.14
Men[b]												
Age	1.03	1.03	1.04									
≥2 diseases	2.04	1.98	2.10	2.81	2.56	3.07	2.25	2.17	2.34	1.94	1.84	2.04
Women[b]												
Age	0.99	0.99	1.00									
≥2 diseases	2.22	2.15	2.30	1.91	1.78	2.04	2.42	2.30	2.54	2.28	2.12	2.44

[a]References are female for sex, no disease for morbidity variables

[b]Reference is no disease for morbidity variables

HR; hazard ratio, CI; confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig. 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl. Table 2
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1, Suppl. Tables 3-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, Fig. 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, Fig. 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063216.R2
Article Type:	Original research
Date Submitted by the Author:	18-Dec-2022
Complete List of Authors:	Saito, Yoshiyuki; The University of Tokyo, Department of Health Economics & Outcomes Research; Kyoto University School of Public Health, Department of Health Informatics Igarashi, Ataru ; The University of Tokyo, Department of Health Economics & Outcomes Research; Yokohama City University School of Medicine Graduate School of Medicine, Unit of Public Health and Preventive Medicine Nakayama, Takeo; Kyoto University School of Public Health, Department of Health Informatics Fukuma, Shingo; Kyoto University, Department of Human Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health economics, Health informatics, Health policy
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors

Yoshiyuki Saito[1,2*] PharmD, Ataru Igarashi[1,3] PhD, Takeo Nakayama[2] MD PhD, Shingo Fukuma[4] MD

Author Affiliations

[1]Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[2]Department of Health Informatics, School of Public Health, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

[3]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa 236-0027, Japan

[4]School of Human Health Sciences, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

Running head

The burden of multimorbidity in Japan 2014-2019

*Corresponding author

Yoshiyuki Saito, PharmD

Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

E-mail: saito.yoshiyuki.86x@kyoto-u.jp

Tel: +81-3-5841-4828

Word count: 3669 (incl. abstract)

Tables: 1

Figures: 3

Supplementary Tables: 4

Abstract

Objective

To describe the prevalence of multimorbidity and its associations with clinical outcomes across age groups.

Design

Retrospective cohort study using nationwide medical claims data.

Setting

Carried out in Japan between April 2014 and March 2019.

Participants

N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE) were included into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals were included into the cohort data set spanning FY2014-FY2018.

Exposures

Multimorbidity was defined as having ≥2 of 15 chronic conditions according to the ICD-10 codes of the Charlson Comorbidity Index.

Primary and Secondary Outcomes

Primary outcome for descriptive analysis: The standardised prevalence of multimorbidity across age groups was evaluated using data from FY 2014 and extrapolated to the Japanese total population. Secondary Outcome for Cox regression model: Hospitalisation or death events were traced by month using medical claims data and insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation and/or death events across age groups were analysed using a Cox regression model.

Results

The standardised prevalence rate of multimorbidity in the nationwide Japanese total population was approximately 5% (ages 25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%),), and 60% (70-74).

Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity had a higher incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41 [95% CI, 3.23-3.53] in ages ≥60). The difference in the incidence of clinical events between multimorbidity and no-multimorbidity was larger than that between age groups.

Conclusions

Multimorbidity is already prevalent in the middle-aged generation and is associated with poor clinical outcomes. These findings underscore the significance of multimorbidity and highlight the urgent need for preventive intervention at the public health care level.

Article Summary

Strengths and limitations of this study

- The current study covers a wide age range of individuals from a nationwide general population.
- Japan`s high medical insurance coverage rate made it possible to comprehensively identify chronic diseases from receipts.
- The longitudinal analysis enabled the examination of clinical outcomes of multiple co-morbidities.
- The prevalence of multimorbidity may be underestimated because the target population comprised regular employees and their families and might accordingly be healthier than the general population.

Keywords

chronic disease, insurance claims, middle age, multimorbidity, preventive medicine

Introduction

Aging societies worldwide face the problem of how to provide adequate and affordable health care for a growing number of patients with multiple chronic conditions, termed multimorbidity.[1,2] Managing multimorbidity is becoming a global challenge on the clinical and public healthcare level not only in high-, but also in low- and middle-income countries.[3] Many epidemiological studies on multimorbidity have shown its association with age, socio-demographic and socio-economic factors.[4-7] In addition, numerous studies have shown that multiple comorbidities are common in older people.[8-11] It has been reported that multimorbid older patients had more than twice as many contacts per year with physicians than those without multimorbidity[12] and that the likelihood of being hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.[8] On the other hand, the accumulation of chronic diseases occurs continuously from middle age. A number of recent studies conducted in various countries have reported that the onset of multimorbidity is shifting towards younger age groups.[6, 13-15] However, multimorbidity studies tend to focus on older people, and in-depth knowledge on multimorbidity in younger age groups is lacking.

Here, to evaluate the current status of multimorbidity across age groups and examine its association with clinical outcomes, we analysed a large nationwide medical claims

cohort. Our findings add to existing knowledge by showing that multimorbidity has a significant impact on health starting from middle age and underscore the need for preventive intervention on the public health care level.

Materials and Methods

Data source

We used the nationwide medical claims and enrolment data of the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE), which is one of the largest social insurance associations in Japan. HIA^{2}CE is a comprehensive insurer which includes 1700 companies, from small engineering companies to middle and large construction companies across Japan. This claims database covers a total of 400 000 insured persons, consisting of employees and their dependents.

The insured-based data base is used widely and one of the popular real-world data in Japan.[16] Japan has maintained a universal health coverage system since 1961. All medical information regarding clinical practice covered by this health insurance is included in the medical claims data, except for self-financed medical care and individuals who receive public assistance. Furthermore, medical facilities have been obliged since 2011 to submit medical claims data as an electronic record. Medical claims data include the names of the diagnosed diseases, the names of medical procedures, and the names of prescribed medications, among others. In the present study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and hospitalisations and deaths from the medical claims data in HIA^{2}CE from FY2014 to

FY2018 (April 2014 to March 2019). The enrolment data from HIA^{2}CE includes the medical characteristics and in-out information of insured persons as of April 2019.

Research design and study population

We prepared two data sets for analysis. The first was a cross-sectional data set containing baseline data of FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The study population for this baseline data set included individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since HIA2CE is a type of insurance for workers in Japan, the database include only under 75 years individuals. Therefore, the maximum age in this cohort was 74 years. Participants younger than 20 in FY2014 as well as participants who died during FY2014 were excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to FY2018 (April 2014 to March 2019). The second data set contained participants insured in whole period. We used this cohort data set to conduct Cox regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).

Definition of diagnosed diseases and multimorbidity

There are a variety of definitions for chronic conditions in multimorbidity studies.[17-19] We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the diseases associated with a significant risk of clinical events.[20] The reason, we used CCI, was that we focused on describing the prevalence of each disease and also assessing the association of multimorbidity on hospitalisation or death. The CCI Canadian version has been reported to be applicable to Japanese claims data.[21] We therefore defined diagnosed diseases using medical claims data following ICD-10 codes of the CCI Canada version. We merged the conditions “diabetes with chronic complication” and “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease” and “moderate or severe liver disease” into “liver disease”. The following 15 chronic conditions were included: AIDS/HIV, any malignancy (including lymphoma and leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour, liver disease, myocardial infarction, peptic ulcer disease, renal disease, and rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in the Supplement. Multimorbidity status was defined as the concurrent presence of two or more (≥2) diagnosed diseases among these conditions.[22, 23] We only used confirmed diagnoses, not including suspected diagnoses, in Japanese claims data.

Definition of outcome events; hospitalisation or death

We defined two composite outcomes, hospitalisation or death, which occurred during the period from FY2015 to FY2018. Using the medical claims data, both events were traced by month. In Japan, the validity of death event information is reported to be less sensitive if derived from medical claims data only.[24, 25] Therefore, we also used death information from enrolment data recorded by the insurer: if either contained death information, this was defined as a death event.

Estimation of diagnosed disease prevalence to a nationwide scale

Diagnosed disease prevalence from baseline data was standardised to the nationwide Japanese total population. We calculated prevalence rates according to groups by 5-year age brackets and sex. Then, we estimated the prevalence rates standardized to Japanese total population (age-sex standardized prevalence rate), using the number from the vital statistics 2014 in Japan.[26]

The association of multimorbidity with outcome by age group

To examine the association of multimorbidity with outcome by age group, we performed Cox regression analysis adjusted by sex using cohort data from four consecutive years (FY2015 to FY2018). The independent and additive effect of multimorbidity and aging, we defined combined categories according to three age groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥60, respectively) and the binary status of multimorbidity, with the reference set as no multimorbidity individuals aged 20-39. This model was able to show HR for aging alone (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-39 ages without multimorbidity).

Statistical analysis

Cox regression was conducted for the association of multimorbidity with outcome by age group. Our hypothesis was aging and MM or these combination leads to worsen clinical events. Therefore, we defined 6 groups which were a combination of 3 categories of generation and MM, and we estimated HR in each group in reference of young (aged 20-39) without MM. Regarding this model, we interpreted both the independent impact of generation and MM on outcomes and the impact of MM in each

generation. Results were considered statistically significant at a two-sided *P*-value of less than 0.05. All analyses were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX, USA).

Patient and Public involvement

Patients or the public were not involved in this research. However, the results of this study will be disseminated to the public through various means including published papers and presentations.

Results

Study participants

We analysed *n* = 246 671 individuals in the baseline data set in FY2014 (Table1) and *n* = 181 959 individuals in the cohort data set FY2014-FY2018. Because the follow-up was four years, the cohort data set was slightly smaller than the baseline data set, especially as a number of young individuals aged 20-24 and older individuals aged >60 dropped out. This may be due to raising children or early retirement, and explains the higher proportion of men in the cohort data set. Mean age and co-morbidity numbers among CCI diseases were mostly comparable between the two data sets, although the prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in disease prevalence between genders were observed. Notably, men had a higher prevalence of diabetes mellitus (*P* = 0.001) whereas women had a higher prevalence of chronic pulmonary disease (*P* = 0.002).

Estimated prevalence of multimorbidity in the Japanese total population

The prevalence of diagnosed diseases in FY2014 was applied to the vital statistics of the Japanese population in 2014. The standardised prevalence of multimorbidity was

estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population (eTable 3A in the Supplement). The prevalence rate with age was increased , i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of diseases as well as the below results are shown in eTable 3B in the Supplement). Figure 2B shows the types of diseases and their prevalence across age groups. The top five diseases across the age groups “young” (20-39), “middle-aged (40-59), and “old” (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, and any malignancy; “middle-aged”: chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-44, the top five accelerating diseases were dementia, cerebrovascular disease, peripheral vascular disease, metastatic tumour, and congestive heart failure.

The association of multimorbidity with outcome by age group.

The composite outcomes occurred 17.2% (death 0.8%, hospitalisation 16.9%) in the follow-up period (eTable2). Cox regression analysis showed that young individuals aged 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages ≥60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with multimorbidity has a risk more than ages ≥60 without multimorbidity.

We also assessed HRs for non-multimorbid and multimorbid women and men separately and found that women had a lower HR than men in the 20-39 age group but a higher HR than men in the ≥60 age group (eTable 4 in the Supplement).

Discussion

In this study we analysed nationwide medical claims data for 15 chronic diseases in a large cohort of the general population of Japan. As key findings, standardised prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for women. Further, age group-specific prevalence rates for multimorbidity ranged from 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an accelerating increase after age 40. Importantly, significant differences in the clinical outcomes of multimorbidity versus no multimorbidity were already present in young and middle-aged individuals.

The present study drew individuals covering a wide age range from a nationwide general population. This allowed us to examine the burden of multiple co-morbidities in young, middle-aged and old age groups in the real world. In addition, because Japan has a high medical insurance coverage rate, it was possible to comprehensively identify chronic diseases from receipts. Further, longitudinal analysis enabled us to examine the clinical outcomes of multiple co-morbidities. With regard to limitations, the target population comprised regular employees and their families and might accordingly be healthier than the general population. Also, we defined multimorbidity by disease list included in CCI most likely to lead to death, hence, we were not able to consider other

diseases associated with health-related quality of life loss. CCI originally includes comorbidities that have a strong impact on mortality, not quality of life and well-being. The presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in individuals already suffering from other chronic diseases,[27] younger people,[28] and people with a low socio-economic status.[29] Such diseases often remain undiagnosed or underreported in health records.[30] Also, we collected diseases which were occurred during the year (FY2014). Therefore, patients who were untreated, undiagnosed, or discontinued treatment cannot be picked up. These limitations likely contributed to an underestimation of multimorbidity in our cohort. Further, because we did not manually verify the presence of disease using the physician's medical records data or medication information, disease names extracted from the medical claims data might be incorrect in some cases. In particular, Japanese physicians sometimes change the name of the disease in the medical record to the "correct" disease name for the medication they wish to prescribe, a practice called "disease name for claims data". Because of differences in data sources and study populations, direct comparison of population-based prevalence rates between studies is not straightforward. Nonetheless, the standardised prevalence rates for multimorbidity as reported in the present study - 26.1% for men and 26.0% for women - are similar to those reported by recent studies in

other high-income countries, such as the United States (25% in men, 25% in women), [31] England (24.4% in men, 30% in women), [32] Canada (24.3% whole population),[5] and Denmark (19.3% in men, 23.7% in women).[6] Also recently some Asian countries reported similar prevalence, Iran (13.4% in men, 25.0% in women),[33] India, and Bangladesh (53.7% - 56.5% in both genders, over aged 60).[34] Many previous studies on multimorbidity focused on the older generation, aged 65 and up, because of the larger number of chronic diseases in this age group and the increasing number of people entering it. However, our present data show that already approximately 10% of 30-34-, 19% of 45-49-, and 33% of 55-59-year-olds have ≥2 chronic diseases. Further, 1% of 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥5 chronic diseases. These results show that multimorbidity is already prominent in the middle-aged population. Recent studies reported similar or slightly higher prevalence rates for ≥2 chronic diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)[29] and a Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)[5] population, although these two studies also included mental diseases and osteoporosis, which our present study did not. Our present study shows that, among 15 chronic diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer

disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes mellitus, the prevalence in the present study is similar to that previously reported in an American population (15-30% in individuals aged 55-65)[29] but higher than that in a Canadian population (16.6% in individuals aged 55-64)[4]. The prevalence of chronic pulmonary disease in our present 55-65-year-olds was almost twice as high as those seen for the combined prevalence of asthma and chronic obstructive pulmonary disease (COPD) in an American population aged 55-65 years (5% for men and 10% for women)[29] and in a Canadian population aged 55-64 years (13.7%).[5] This difference might have arisen due to our inclusion of various other pulmonary diseases besides asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in the present study was comparable to that seen in an adult population in Northern Italy[35] and in an adult population in Korea,[36] although this comparison requires care since the types of liver disease in these studies and the age groups included vary.

Analysis of clinical outcomes using Cox regression revealed that the presence of multimorbidity increased HRs in all age groups, including young individuals. In addition, the comparison of the increased HRs resulting from multimorbidity versus no multimorbidity showed that the impact of multimorbidity exceeds that of increasing age. These results indicate that multimorbidity places a burden on all age groups.

Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and any malignancy) in the present study are lifestyle-related diseases that develop slowly over time. This trend should be greeted with alarm. We trust that this study raises awareness of the potential health risks and burden associated with the early onset of multimorbidity in young and middle-aged, the period when one is busy working and raising children. Future studies should investigate the specific lifestyle factors associated with an elevated risk of multimorbidity in the Japanese working population. Ultimately, public health care policies should be aimed at efforts to reverse the trend toward early multimorbidity onset.

In conclusion, the present study confirmed the prevalence of MM by including in the denominator those who did not have the receipt of medical claims and to estimate the prevalence of MM in the general population. Furthermore, we revealed that the impact of multimorbidity is already clinically significant in middle-aged Japanese, with elevated adverse events such as hospitalisation or death. In addition, the risk posed by multimorbidity exceeds that of aging in all age groups. These results underscore the need to undertake healthcare intervention against the onset of multimorbidity before middle-aged, and not to leave it as a problem for geriatricians.

Ethical Approval

The present study was approved by the Institutional Review Board (IRB) of Kyoto University (approval number: R0817). All data were anonymised before analysis and none of the researchers had access to patient-identifiable information. The IRB waived informed consent for this observational study.

Data Availability Statement

All data are incorporated into the article and its online supplementary material.

Author Contributions

Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS. Administrative, technical, or material support: YS, SF. Study supervision: SF, AI, TN. YS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval and agreed to be accountable for all aspects of work.

Acknowledgements

The authors are grateful to HIA^{2}CE for providing data for the present study.

Funding

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in the design of the study; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Competing Interests

None declared.

Patient Consent for Publication

Not applicable.

Figure Legends

Figure 1. Participant selection flowchart. FY; fiscal year

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A**) Percentage of the population having 0 to ≥5 chronic diseases by age group. **B**) Prevalence of the top ten chronic diseases by age group. **C**) The top ten chronic diseases with the steepest increase after age 40-44 years.

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

References

1 Bleich SN, Sherrod C, Chiang A*, et al*. Systematic Review of Programs Treating High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities in the United States, 2008-2014. *Prev Chronic Dis*. Nov 12 2015;12:E197. doi:10.5888/pcd12.150275

2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. *Prev Med Rep*. Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008

3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y, Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of

multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614. doi:10.1371/journal.pone.0243614

4 Low LL, Kwan YH, Ko MSM*, et al*. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245. doi:10.1001/jamanetworkopen.2019.15245

5 Pefoyo AJ, Bronskill SE, Gruneir A*, et al*. The increasing burden and complexity of multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-1733-2

6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8

7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of multimorbidity on healthcare utilisation and work productivity by socioeconomic groups: Cross-sectional analyses of Australia and Japan. *PLoS One*. 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281

8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. *BMC Health Serv Res*. Jan 22 2015;15:23. doi:10.1186/s12913-015-0698-2

9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-

sectional study based on nationwide claims data. *BMJ Open*. Jun 9 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333

10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812. doi:10.1136/bmjopen-2016-012812

11 Picco L, Achilla E, Abdin E*, et al*. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10 2016;16:173. doi:10.1186/s12913-016-1421-7

12 van den Bussche H, Schon G, Kolonko T*, et al*. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54

13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152. doi:10.1186/s12916-017-0913-6

14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising burden of multimorbidity and related socio-demographic factors: a repeated cross-sectional study of Ontarians. *Can J Public Health*. Apr 13 2021;doi:10.17269/s41997-021-00474-y

15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the

ageing population of England, 2002-2015. *J Comorb*. Jan-Dec 2019;9:2235042X19872030. doi:10.1177/2235042X19872030

16 Katsutoshi H, Annabel B, Yasuhiko M, et al. Current Status, Challenges, and Future Perspectives of Real-World Data and Real-World Evidence in Japan. *Drugs - Real World Outcomes.* 2021;8:459–480. doi:org/10.1007/s40801-021-00266-3

17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments used for measuring the association of the level of multimorbidity and clinically important outcomes. *BMJ Open*. 2021;May 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.

18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.

19 Jürisson M, Heti P, Anneli U, et al. Prevalence of chronic conditions and multimorbidity in Estonia: a population-based cross-sectional study. *BMJ Open.* 2021;Oct 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.

20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan H, Li B, Couris CM*, et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*. 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.

22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*. Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098

23 Le Reste JY, Nabbe P, Manceau B*, et al*. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001

24 Ooba N, Setoguchi S, Ando T*, et al*. Claims-based definition of death in Japanese claims database: validity and implications. *PLoS One*. 2013;8(5):e66116. doi:10.1371/journal.pone.0066116

25 Sakai M, Ohtera S, Iwao T*, et al*. Validation of claims data to identify death among aged persons utilizing enrollment data from health insurance unions. *Environ Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3

26 Statistics Bureau of Japan. Preliminary count of the Japanese population. Accessed March, 2014. http://www.stat.go.jp/data/jinsui/index.html

27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234

28 Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost

productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002

29 Rocca WA, Boyd CM, Grossardt BR*, et al*. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49. doi:10.1016/j.mayocp.2014.07.010

30 Cassell A, Edwards D, Harshfield A*, et al*. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. Apr 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465

31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E*, et al*. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251

32 St Sauver JL, Boyd CM, Grossardt BR*, et al*. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413

33 Masoomeh A, Azam M, Mehdi Y. et al. Multimorbidity as an important issue among women: results of a gender difference investigation in a large population-based cross-sectional study in West Asia. *BMJ Open*. 2017;May 9;7(5):e013548. doi: 10.1136/bmjopen-2016-013548.

34 Sanghamitra P, Subhashisa S, Mohammad AH, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review bmj open. *BMJ Open*. 2015 Oct 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.

35 Bellentani S, Tiribelli C, Saccoccio G*, et al*. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec 1994;20(6):1442-9. doi:10.1002/hep.1840200611

36 Park SH, Plank LD, Suk KT*, et al*. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr 2020;26(2):209-215. doi:10.3350/cmh.2019.0065

Supplementary Information

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population

	Baseline data in FY2014					
	Overall		**Men**		**Women**	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%
Men	144,237	58.5	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8
20-24	18,524	7.5	11,315	7.8	7,209	7.0
25-29	17,251	7.0	12,014	8.3	5,237	5.1
30-34	18,093	7.3	11,104	7.7	6,989	6.8
35-39	23,878	9.7	13,278	9.2	10,600	0.3
40-44	39,721	16.1	21,640	15.0	18,081	17.7
45-49	40,908	16.6	24,191	16.8	16,717	16.3
50-54	29,466	11.9	17,577	12.2	11,889	11.6
55-59	20,149	8.2	11,343	7.9	8,806	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4
65-69	11,931	4.8	6,768	4.7	5,163	5.0
70-74	5,472	2.2	2,301	1.6	3,171	3.1
AIDS/HIV	96	0.0	62	0.0	34	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9
Dementia	447	0.2	210	0.1	237	0.2
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6
Renal disease	2,573	1.0	1,751	1.2	822	0.8
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3
Disease no. among CCI						
no disease	171,140	69.4	101,857	70.6	69,283	67.6
1 disease	22,947	9.3	12,032	8.3	10,915	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7
Multimorbidity (≥2 diseases among CCI)	52,584	21.3	30,348	21.0	22,236	21.7

Values are numbers (%) unless otherwise stated.
[a] Any malignancy includes leukemia and lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

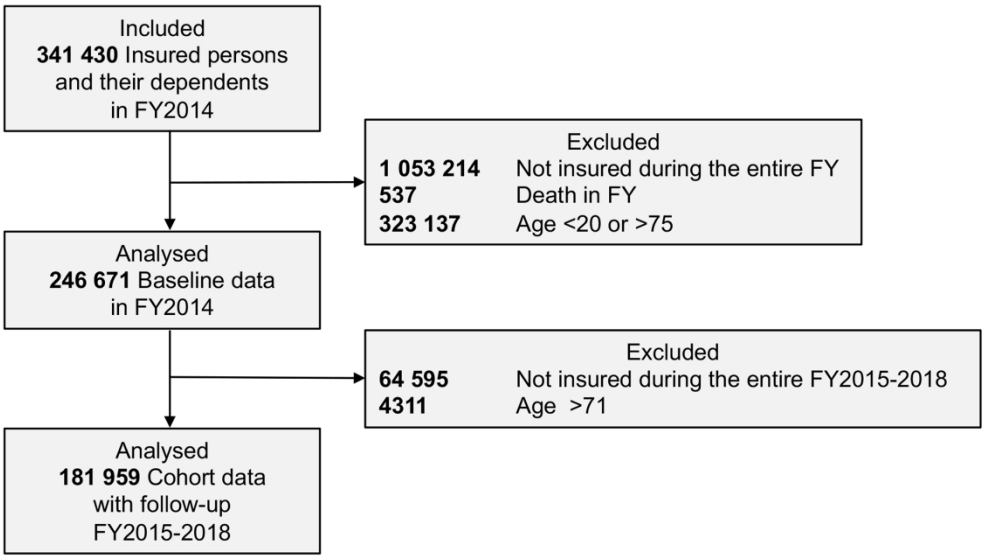

Figure 1. Participant selection flowchart. FY; fiscal year

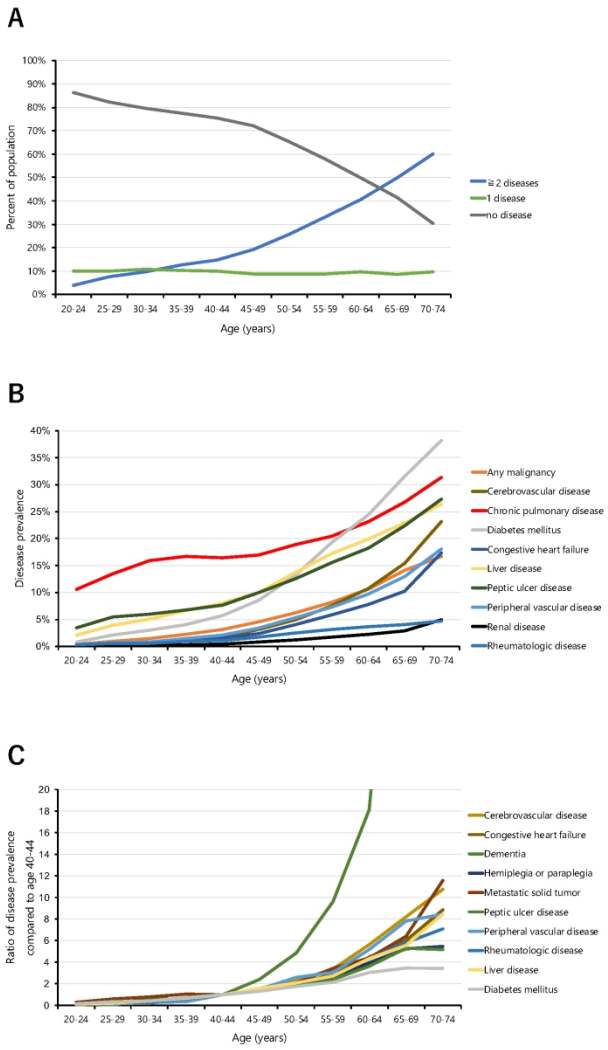

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥5 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44 years.

297x420mm (200 x 200 DPI)

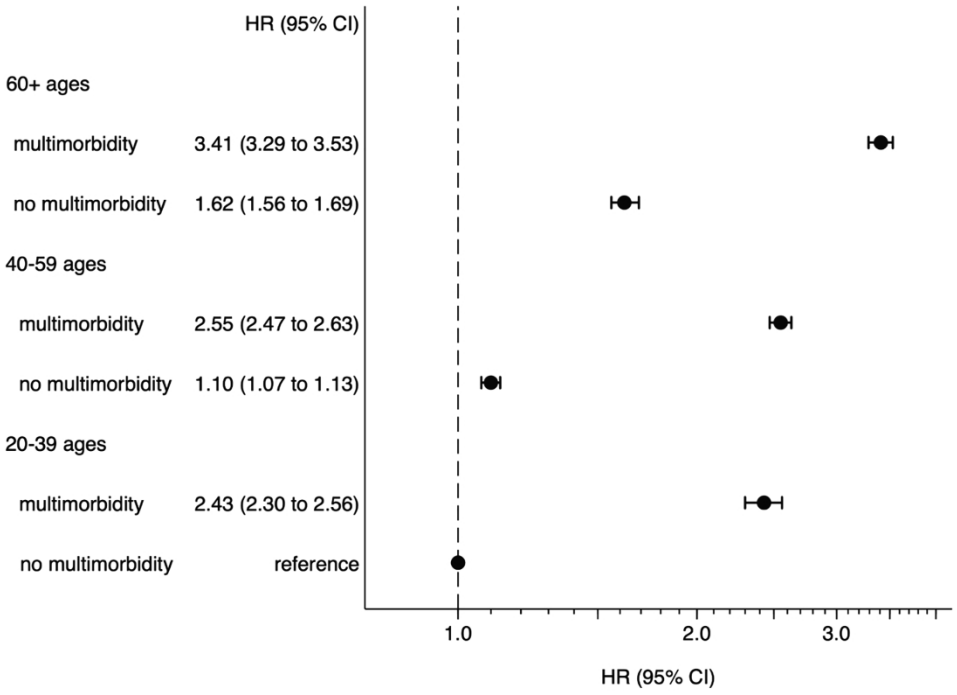

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

Supplementary material

Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Diseases	ICD-10 codes
AIDS/HIV	B20.x-B22.x, B24.x
Any malignancy, incl. leukemia and lymphoma	C00.x-C26.x, C30.x-C34.x, C37.x-C41x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.3, C88.7, C88.9, C90.0, C90.1, C91.x- C93.x, C94.0-C94.3, C94.5, C94.7, C95.x, C96.x, C43.x, C88.0-C88.2, C90.2, C94.4, C97.x
Cerebrovascular disease	I69.x, G45.x, G46.x, H34.0, I60.x-I68.x
Chronic pulmonary disease	J41.x-J47.x, J60.x-J66.x, I27.8, I27.9, J40.x, J67.x, J68.4, J70.1, J70.3
Congestive heart failure	I50.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5- I42.9, I43.x, P29.0
Dementia	F00.x-F02.x, F03.x, F05.1, G30.x, G31.1
Diabetes with chronic complication	E10.2-E10.4, E11.2-E11.4, E13.2-E13.4, E14.2-E14.4, E10.5, E10.7, E11.5, E11.7, E12.2-E12.5, E12.7, E13.5, E13.7, E14.5, E14.7
Diabetes without chronic complication	E10.1, E10.9, E11.1, E11.9, E13.1, E13.9, E14.1, E14.9, E10.0, E10.6, E10.8, E11.0, E11.6, E11.8, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.6, E13.8, E14.0, E14.6, E14.8
Hemiplegia or paraplegia	G81.x, G82.0-G82.2, G04.1, G11.4, G80.1, G80.2, G82.3-G82.5, G83.0-G83.4, G83.9
Metastatic solid tumor	C77.x-C79.x, C80.x
Mild liver disease	K70.3, K71.7, K73.x, K74.3- K74.6, B18.x, K70.0-K70.2, K70.9, K71.3-K71.5, K74.0-K74.2, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	K72.1, K72.9, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K76.5
Myocardial infarction	I25.2, I21.x, I22.x
Peptic ulcer disease	K25.4-K25.7, K26.4-K26.7, K27.4-K27.7, K28.4-K28.7, K25.0-K25.3, K25.9, K26.0-K26.3, K26.9, K27.0-K27.3, K27.9, K28.0-K28.3, K28.9
Peripheral vascular disease	I71.x, I73.9, Z95.8, Z95.9, I70.x, I73.1, I73.8, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9

Renal disease	N18.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Rheumatology disease	M05.x, M06.0, M32.x, M33.2, M34.x, M35.3, M06.1-M06.4, M06.8, M06.9, M31.5, M33.0, M33.1, M33.9, M35.1, M36.0

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

	Baseline data in FY2014		Cohort data		*P*-value[c]
N	242,360	(100%)	181,959	(100%)	
Men	142,471	(58.8%)	111,088	(61.1%)	<0.01
Age (Mean, SD)	44.5	(12.5)	44.7	(10.6)	<0.01
20-24	18,524	(7.6%)	5,052	(2.8%)	<0.01
25-29	17,251	(7.1%)	12,675	(7.0%)	
30-34	18,093	(7.5%)	14,784	(8.1%)	
35-39	23,878	(9.9%)	20,508	(11.3%)	
40-44	39,721	(16.4%)	35,168	(19.3%)	
45-49	40,908	(16.9%)	37,124	(20.4%)	
50-54	29,466	(12.2%)	25,906	(14.2%)	
55-59	20,149	(8.3%)	13,052	(7.2%)	
60-64	21,278	(8.8%)	10,735	(5.9%)	
65-69	11,931	(4.9%)	6,246	(3.4%)	
70-71	1,161	(0.5%)	709	(0.4%)	
AIDS/HIV	94	(0.0%)	74	(0.0%)	0.76
Any malignancy[a]	11,343	(4.7%)	8,377	(4.6%)	0.24
Cerebrovascular disease	9,860	(4.1%)	6,971	(3.8%)	<0.01
Chronic pulmonary disease	41,866	(17.3%)	32,093	(17.6%)	<0.01
Congestive heart failure	7,751	(3.2%)	5,710	(3.1%)	0.27
Dementia	291	(0.1%)	190	(0.1%)	0.13
Diabetes mellitus	25,716	(10.6%)	18,755	(10.3%)	<0.01
Hemiplegia or paraplegia	729	(0.3%)	507	(0.3%)	0.19

Liver disease	25,999	(10.7%)	19,725	(10.8%)	0.24
Metastatic solid tumor	2,381	(1.0%)	1,823	(1.0%)	0.53
Myocardial infarction	1,526	(0.6%)	1,092	(0.6%)	0.22
Peptic ulcer disease	24,859	(10.3%)	18,594	(10.2%)	0.68
Peripheral vascular disease	9,623	(4.0%)	7,083	(3.9%)	0.20
	Baseline data in FY2014		**Cohort data**		***P*-value[c]**
N	242,360	(100%)	181,959	(100%)	
Renal disease	2,350	(1.0%)	1,747	(1.0%)	0.75
Rheumatologic disease	3,931	(1.6%)	2,926	(1.6%)	0.72
At least one disease among the top five[b]	69,014	(28.5%)	50,660	(27.8%)	<0.01
Disease no. among CCI (Mean, SD)	0.8	(1.6)	0.8	(1.6)	0.16
0 disease	169,872	(70.1%)	129,037	(70.9%)	<0.01
1 disease	22,514	(9.3%)	15,532	(8.5%)	
2 diseases	16,605	(6.9%)	12,375	(6.8%)	
3 diseases	12,242	(5.1%)	9,046	(5.0%)	
4 diseases	9,076	(3.7%)	6,816	(3.7%)	
≥ 5 diseases	12,051	(5.0%)	9,153	(5.0%)	
Multimorbidity (≥2 diseases among CCI)	49,974	(20.6%)	37,390	(20.5%)	
Composite outcomes	36,893	(15.2%)	31,224	(17.2%)	<0.01
Death	1,507	(0.6%)	1,507	(0.8%)	
Hospitalisation	36,495	(15.1%)	30,826	(16.9%)	

[a] Any malignancy includes leukemia and lymphoma.

[b] Top 5 diseases include chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and cerebrovascular disease.

SD; standard deviation, CCI; Charlson Comorbidity Index
[c] Age (Mean) and Co-morbidity no. (Mean): Student`s t-test. All other variables: Pearson's chi-square test.

Supplementary eTable 3A. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population by gender

	Baseline data in FY2014						Japanese total population					
	Overall		Men		Women		Overall		Men		Women	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%	*N*=88,923,000	%	*N*=44,288,000	%	*N*=44,640,000	%
Men	144,237	58.5	-	-	-	-	44,288,000	49.8	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8	48.0	15.3	47.7	15.3	48.4	15.4
20-24	18,524	7.5	11,315	7.8	7,209	7.0	6,203,000	7.0	3,192,000	7.2	3,012,000	6.7
25-29	17,251	7.0	12,014	8.3	5,237	5.1	6,677,000	7.5	3,414,000	7.7	3,264,000	7.3
30-34	18,093	7.3	11,104	7.7	6,989	6.8	7,466,000	8.4	3,788,000	8.6	3,680,000	8.2
35-39	23,878	9.7	13,278	9.2	10,600	0.3	8,670,000	9.8	4,394,000	9.9	4,276,000	9.6
40-44	39,721	16.1	21,640	15.0	18,081	17.7	9,793,000	11.0	4,956,000	11.2	4,837,000	10.8
45-49	40,908	16.6	24,191	16.8	16,717	16.3	8,609,000	9.7	4,329,000	9.8	4,278,000	9.6
50-54	29,466	11.9	17,577	12.2	11,889	11.6	7,790,000	8.8	3,903,000	8.8	3,887,000	8.7
55-59	20,149	8.2	11,343	7.9	8,806	8.6	7,653,000	8.6	3,802,000	8.6	3,853,000	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4	8,979,000	0.1	4,406,000	9.9	4,573,000	10.2
65-69	11,931	4.8	6,768	4.7	5,163	5.0	9,155,000	10.3	4,414,000	10.0	4,741,000	10.6
70-74	5,472	2.2	2,301	1.6	3,171	3.1	7,928,000	8.9	3,690,000	8.3	4,239,000	9.5
AIDS/ HIV	96	0.0	62	0.0	34	0.0	34,034	0.0	18,979	0.0	15,055	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3	5,775,260	6.5	2,668,349	6.0	3,106,911	7.0
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3	5,773,295	6.5	3,023,765	6.8	2,749,530	6.2
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2	17,303,735	19.5	7,713,864	17.4	9,589,871	21.5
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9	4,317,076	4.9	2,459,170	5.6	1,857,906	4.2
Deme ntia	447	0.2	210	0.1	237	0.2	410,326	0.5	179,350	0.4	230,976	0.5
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2	12,689,040	14.3	7,122,240	16.1	5,566,801	12.5
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3	424,609	0.5	253,040	0.6	171,569	0.4
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9	11,341,444	2.8	6,031,029	13.6	5,310,415	11.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2	1,235,336	1.4	598,734	1.4	636,601	1.4
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3	769,977	0.9	575,894	1.3	194,083	0.4
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3	11,238,524	12.6	5,485,994	12.4	5,752,530	12.9
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6	5,197,644	5.8	2,503,359	5.7	2,694,285	6.0
Renal disease	2,573	1.0	1,751	1.2	822	0.8	1,261,138	1.4	784,770	1.8	476,367	1.1
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7	1,928,685	2.2	530,072	1.2	1,398,613	3.1
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3	30,041,150	33.8	14,676,045	33.1	15,365,106	34.4
Disease no. among CCI												
no disease	171,140	69.4	101,857	70.6	69,283	67.6	57,293,691	64.4	29,006,814	65.5	28,286,877	63.4
1 disease	22,947	9.3	12,032	8.3	10,915	10.7	8,464,436	9.5	3,702,220	8.4	4,762,216	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9	6,799,080	7.6	3,029,535	6.8	3,769,544	8.4
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4	5,534,827	6.2	2,652,231	6.0	2,882,596	6.5
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6	4,261,753	4.8	2,242,062	5.1	2,019,691	4.5
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7	6,574,213	7.4	3,655,138	8.3	2,919,075	6.5
Multimorbidity	52,584	21.3	30,348	21.0	22,236	21.7	23,169,873	26.1	11,578,966	26.1	11,590,906	26.0

(≥2 diseases among CCI)

Values are numbers (%) unless otherwise

[a] Any malignancy includes leukemia and lymphoma.

FY; fiscal year

SD; standard deviation

CCI; Charlson Comorbidity Index

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		20-24		25-29		30-34	
	88,923,000	(100%)	6,204,000	(100%)	6,678,000	(100%)	7,468,000	(100%)
Men	44,288,000	(49.8%)	3,192,000	(51.5%)	3,414,000	(51.1%)	3,788,000	(50.7%)
AIDS/HIV	34,034	(0.0%)	1,400	(0.0%)	1,137	(0.0%)	1,394	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	24,047	(0.4%)	60,604	(0.9%)	103,907	(1.4%)
Cerebrovascular disease	5,773,295	(6.5%)	12,484	(0.2%)	23,767	(0.4%)	40,440	(0.5%)
Chronic pulmonary disease	17,303,735	(19.5%)	656,012	(10.6%)	901,156	(13.5%)	1,184,702	(15.9%)
Congestive heart failure	4,317,076	(4.9%)	21,322	(0.3%)	34,950	(0.5%)	52,469	(0.7%)
Dementia	410,326	(0.5%)	418	(0.0%)	0	(0.0%)	1,053	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	50,290	(0.8%)	141,852	(2.1%)	228,348	(3.1%)
Hemiplegia or paraplegia	424,609	(0.5%)	3,782	(0.1%)	7,489	(0.1%)	10,227	(0.1%)
Liver disease	11,341,444	(12.8%)	129,091	(2.1%)	259,190	(3.9%)	380,993	(5.1%)
Metastatic solid tumor	1,235,336	(1.4%)	6,706	(0.1%)	9,643	(0.1%)	15,804	(0.2%)
Myocardial infarction	769,977	(0.9%)	3,510	(0.1%)	3,859	(0.1%)	7,438	(0.1%)
Peptic ulcer disease	11,238,524	(12.6%)	213,860	(3.4%)	364,164	(5.5%)	444,445	(6.0%)
Peripheral vascular disease	5,197,644	(5.8%)	20,276	(0.3%)	42,759	(0.6%)	60,055	(0.8%)
Renal disease	1,261,138	(1.4%)	6,164	(0.1%)	11,118	(0.2%)	19,957	(0.3%)
Rheumatologic disease	1,928,685	(2.2%)	17,602	(0.3%)	35,051	(0.5%)	43,777	(0.6%)
no disease	57,293,691	(64.4%)	5,352,990	(86.3%)	5,500,039	(82.4%)	5,935,225	(79.5%)
1 disease	8,464,436	(9.5%)	609,768	(9.8%)	666,087	(10.0%)	805,022	(10.8%)
2 diseases	6,799,080	(7.6%)	163,269	(2.6%)	310,407	(4.6%)	399,222	(5.3%)
3 diseases	5,534,827	(6.2%)	45,066	(0.7%)	104,758	(1.6%)	178,423	(2.4%)
4 diseases	4,261,753	(4.8%)	19,190	(0.3%)	52,301	(0.8%)	77,876	(1.0%)
≥ 5 diseases	6,574,213	(7.4%)	13,716	(0.2%)	44,409	(0.7%)	72,233	(1.0%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	241,241	(3.9%)	511,875	(7.7%)	727,754	(9.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		35-39		40-44		45-49	
	88,923,000	(100%)	8,670,000	(100%)	9,793,000	(100%)	8,607,000	(100%)
Men	44,288,000	(49.8%)	4,394,000	(50.7%)	4,956,000	(50.6%)	4,329,000	(50.3%)
AIDS/HIV	34,034	(0.0%)	4,592	(0.1%)	4,124	(0.0%)	3,069	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	198,069	(2.3%)	308,591	(3.2%)	393,299	(4.6%)
Cerebrovascular disease	5,773,295	(6.5%)	93,413	(1.1%)	170,645	(1.7%)	265,098	(3.1%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,446,109	(16.7%)	1,613,639	(16.5%)	1,462,084	(17.0%)
Congestive heart failure	4,317,076	(4.9%)	90,394	(1.0%)	155,193	(1.6%)	201,862	(2.3%)
Dementia	410,326	(0.5%)	734	(0.0%)	1,490	(0.0%)	3,606	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	352,333	(4.1%)	553,455	(5.7%)	737,731	(8.6%)
Hemiplegia or paraplegia	424,609	(0.5%)	13,621	(0.2%)	12,793	(0.1%)	19,669	(0.2%)
Liver disease	11,341,444	(12.8%)	577,316	(6.7%)	784,095	(8.0%)	858,769	(10.0%)
Metastatic solid tumor	1,235,336	(1.4%)	29,912	(0.3%)	56,656	(0.6%)	78,055	(0.9%)
Myocardial infarction	769,977	(0.9%)	8,925	(0.1%)	25,198	(0.3%)	37,793	(0.4%)
Peptic ulcer disease	11,238,524	(12.6%)	589,633	(6.8%)	749,581	(7.7%)	856,494	(10.0%)
Peripheral vascular disease	5,197,644	(5.8%)	127,339	(1.5%)	201,866	(2.1%)	288,167	(3.3%)
Renal disease	1,261,138	(1.4%)	30,634	(0.4%)	46,209	(0.5%)	73,397	(0.9%)
Rheumatologic disease	1,928,685	(2.2%)	79,300	(0.9%)	108,081	(1.1%)	143,756	(1.7%)
no disease	57,293,691	(64.4%)	6,707,086	(77.4%)	7,389,249	(75.5%)	6,205,507	(72.1%)
1 disease	8,464,436	(9.5%)	879,686	(10.1%)	969,263	(9.9%)	762,446	(8.9%)
2 diseases	6,799,080	(7.6%)	529,075	(6.1%)	633,182	(6.5%)	588,650	(6.8%)
3 diseases	5,534,827	(6.2%)	284,566	(3.3%)	352,334	(3.6%)	416,546	(4.8%)
4 diseases	4,261,753	(4.8%)	152,965	(1.8%)	232,087	(2.4%)	297,143	(3.5%)
≥ 5 diseases	6,574,213	(7.4%)	116,621	(1.3%)	216,885	(2.2%)	336,707	(3.9%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	1,083,227	(12.5%)	1,434,488	(14.6%)	1,639,046	(19.0%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		50-54		55-59		60-64	
	88,923,000	(100%)	7,790,000	(100%)	7,655,000	(100%)	8,979,000	(100%)
Men	44,288,000	(49.8%)	3,903,000	(50.1%)	3,802,000	(49.7%)	4,406,000	(49.1%)
AIDS/HIV	34,034	(0.0%)	2,979	(0.0%)	3,324	(0.0%)	5,281	(0.1%)
Any malignancy[a]	5,775,260	(6.5%)	483,592	(6.2%)	624,101	(8.2%)	958,696	(10.7%)
Cerebrovascular disease	5,773,295	(6.5%)	387,663	(5.0%)	573,513	(7.5%)	965,151	(10.7%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,469,169	(18.9%)	1,565,078	(20.4%)	2,074,822	(23.1%)
Congestive heart failure	4,317,076	(4.9%)	316,491	(4.1%)	443,956	(5.8%)	694,542	(7.7%)
Dementia	410,326	(0.5%)	7,254	(0.1%)	14,375	(0.2%)	27,048	(0.3%)
Diabetes mellitus	12,689,040	(14.3%)	1,028,899	(13.2%)	1,477,049	(19.3%)	2,197,472	(24.5%)
Hemiplegia or paraplegia	424,609	(0.5%)	26,826	(0.3%)	43,702	(0.6%)	56,416	(0.6%)
Liver disease	11,341,444	(12.8%)	1,063,948	(13.7%)	1,316,086	(17.2%)	1,785,515	(19.9%)
Metastatic solid tumor	1,235,336	(1.4%)	104,654	(1.3%)	136,279	(1.8%)	204,377	(2.3%)
Myocardial infarction	769,977	(0.9%)	65,457	(0.8%)	76,970	(1.0%)	130,757	(1.5%)
Peptic ulcer disease	11,238,524	(12.6%)	977,192	(12.5%)	1,190,533	(15.6%)	1,633,285	(18.2%)
Peripheral vascular disease	5,197,644	(5.8%)	411,839	(5.3%)	554,776	(7.2%)	876,673	(9.8%)
Renal disease	1,261,138	(1.4%)	95,578	(1.2%)	126,432	(1.7%)	202,057	(2.3%)
Rheumatologic disease	1,928,685	(2.2%)	191,910	(2.5%)	235,332	(3.1%)	326,918	(3.6%)
no disease	57,293,691	(64.4%)	5,087,646	(65.3%)	4,435,684	(57.9%)	4,468,987	(49.8%)
1 disease	8,464,436	(9.5%)	687,805	(8.8%)	680,727	(8.9%)	859,388	(9.6%)
2 diseases	6,799,080	(7.6%)	631,794	(8.1%)	687,732	(9.0%)	933,542	(10.4%)
3 diseases	5,534,827	(6.2%)	510,570	(6.6%)	638,438	(8.3%)	881,741	(9.8%)
4 diseases	4,261,753	(4.8%)	382,265	(4.9%)	509,123	(6.7%)	729,058	(8.1%)
≥ 5 diseases	6,574,213	(7.4%)	489,921	(6.3%)	703,297	(9.2%)	1,106,284	(12.3%)

Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	2,014,550	(25.9%)	2,538,590	(33.2%)	3,650,625	(40.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		65-69		70-74	
	88,923,000	(100%)	9,155,000	(100%)	7,929,000	(100%)
Men	44,288,000	(49.8%)	4,414,000	(48.2%)	3,690,000	(46.5%)
AIDS/HIV	34,034	(0.0%)	3,793	(0.0%)	2,940	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	1,296,908	(14.2%)	1,323,445	(16.7%)
Cerebrovascular disease	5,773,295	(6.5%)	1,404,663	(15.3%)	1,836,456	(23.2%)
Chronic pulmonary disease	17,303,735	(19.5%)	2,445,425	(26.7%)	2,485,540	(31.3%)
Congestive heart failure	4,317,076	(4.9%)	931,107	(10.2%)	1,374,790	(17.3%)
Dementia	410,326	(0.5%)	83,286	(0.9%)	271,063	(3.4%)
Diabetes mellitus	12,689,040	(14.3%)	2,891,848	(31.6%)	3,029,762	(38.2%)
Hemiplegia or paraplegia	424,609	(0.5%)	81,998	(0.9%)	148,087	(1.9%)
Liver disease	11,341,444	(12.8%)	2,094,406	(22.9%)	2,092,035	(26.4%)
Metastatic solid tumor	1,235,336	(1.4%)	300,280	(3.3%)	292,970	(3.7%)
Myocardial infarction	769,977	(0.9%)	197,033	(2.2%)	213,037	(2.7%)
Peptic ulcer disease	11,238,524	(12.6%)	2,053,538	(22.4%)	2,165,800	(27.3%)
Peripheral vascular disease	5,197,644	(5.8%)	1,181,335	(12.9%)	1,432,557	(18.1%)
Renal disease	1,261,138	(1.4%)	257,988	(2.8%)	391,604	(4.9%)
Rheumatologic disease	1,928,685	(2.2%)	374,826	(4.1%)	372,134	(4.7%)
no disease	57,293,691	(64.4%)	3,803,485	(41.5%)	2,407,794	(30.4%)
1 disease	8,464,436	(9.5%)	785,842	(8.6%)	758,403	(9.6%)
2 diseases	6,799,080	(7.6%)	1,013,307	(11.1%)	908,900	(11.5%)
3 diseases	5,534,827	(6.2%)	1,074,487	(11.7%)	1,047,899	(13.2%)
4 diseases	4,261,753	(4.8%)	886,159	(9.7%)	923,584	(11.6%)

≥ 5 diseases	6,574,213	(7.4%)	1,591,721	(17.4%)	1,882,418	(23.7%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	4,565,674	(49.9%)	4,762,801	(60.1%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Overall[a]												
	Full Model			**20-39 years**			**40-59 years**			**60-71 years**		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	1.02	1.01	1.02									
Sex	0.97	0.95	0.99	0.36	0.34	0.37	1.29	1.25	1.33	1.44	1.38	1.51
≥2 diseases	2.17	2.12	2.21	2.17	2.05	2.29	2.31	2.24	2.38	2.05	1.97	2.14
Men[b]												
Age	1.03	1.03	1.04									
≥2 diseases	2.04	1.98	2.10	2.81	2.56	3.07	2.25	2.17	2.34	1.94	1.84	2.04
Women[b]												
Age	0.99	0.99	1.00									
≥2 diseases	2.22	2.15	2.30	1.91	1.78	2.04	2.42	2.30	2.54	2.28	2.12	2.44

[a]References are female for sex, no disease for morbidity variables

[b]Reference is no disease for morbidity variables

HR; hazard ratio, CI; confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig. 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl. Table 2
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1, Suppl. Tables 3-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, Fig. 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, Fig. 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063216.R3
Article Type:	Original research
Date Submitted by the Author:	06-Apr-2023
Complete List of Authors:	Saito, Yoshiyuki; The University of Tokyo, Department of Health Economics & Outcomes Research; Kyoto University School of Public Health, Department of Health Informatics Igarashi, Ataru ; The University of Tokyo, Department of Health Economics & Outcomes Research; Yokohama City University School of Medicine Graduate School of Medicine, Unit of Public Health and Preventive Medicine Nakayama, Takeo; Kyoto University School of Public Health, Department of Health Informatics Fukuma, Shingo; Kyoto University, Department of Human Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health economics, Health informatics, Health policy
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title

The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors

Yoshiyuki Saito[1,2*] PharmD, Ataru Igarashi[1,3] PhD, Takeo Nakayama[2] MD PhD, Shingo Fukuma[4] MD

Author Affiliations

[1]Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[2]Department of Health Informatics, School of Public Health, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

[3]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa 236-0027, Japan

[4]School of Human Health Sciences, Graduate School of Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

Running head

The burden of multimorbidity in Japan 2014-2019

*Corresponding author

Yoshiyuki Saito, PharmD

Department of Health Economics & Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

E-mail: saito.yoshiyuki.86x@kyoto-u.jp

Tel: +81-3-5841-4828

Word count: 3638 (incl. abstract)

Tables: 1

Figures: 3

Supplementary Tables: 4

Abstract

Objective

To describe the prevalence of multimorbidity and its associations with clinical outcomes across age groups.

Design

Retrospective cohort study using nationwide medical claims data.

Setting

Carried out in Japan between April 2014 and March 2019.

Participants

N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance were included into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals were included into the cohort data set spanning FY2014-FY2018.

Exposures

Multimorbidity was defined as having ≥2 of 15 chronic conditions according to the ICD-10 codes of the Charlson Comorbidity Index.

Primary and Secondary Outcomes

Primary outcome: The standardised prevalence of multimorbidity across age groups was evaluated using data from FY 2014 and extrapolated to the Japanese total

population. Secondary Outcome: Hospitalisation or death events were traced by month using medical claims data and insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation and/or death events across age groups were analysed using a Cox regression model.

Results

The standardised prevalence rate of multimorbidity in the nationwide Japanese total population was estimated to 26.1%. The prevalence rate with age was increased, approximately 5%(ages 20-29), 10%(30-39), 20%(40-49), 30%(50-59), 50%(60-69), and 60%(70-74). Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity had a higher incidence of clinical events in any age group(HR = 2.43 [95% CI, 2.30-2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41[95% CI, 3.23-3.53] in ages ≥60). The difference in the incidence of clinical events between multimorbidity and no-multimorbidity was larger than that between age groups.

Conclusions

Multimorbidity is already prevalent in the middle-aged generation and is associated with poor clinical outcomes. These findings underscore the significance of multimorbidity and highlight the urgent need for preventive intervention at the public health care level.

Article Summary

Strengths and limitations of this study

- The current study covers a wide age range of individuals from a nationwide general population.
- Japan`s high medical insurance coverage rate made it possible to comprehensively identify chronic diseases from receipts.
- The longitudinal analysis enabled the examination of clinical outcomes of multiple co-morbidities.
- The prevalence of multimorbidity may be underestimated because the target population comprised regular employees and their families and might accordingly be healthier than the general population.

Keywords

chronic disease, insurance claims, middle age, multimorbidity, preventive medicine

Introduction

Aging societies worldwide face the problem of how to provide adequate and affordable health care for a growing number of patients with multiple chronic conditions, termed multimorbidity.[1,2] Managing multimorbidity is becoming a global challenge on the clinical and public healthcare level not only in high-, but also in low- and middle-income countries.[3] Many epidemiological studies on multimorbidity have shown its association with age, socio-demographic and socio-economic factors.[4-7] In addition, numerous studies have shown that multiple comorbidities are common in older people.[8-11] It has been reported that multimorbid older patients had more than twice as many contacts per year with physicians than those without multimorbidity[12] and that the likelihood of being hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.[8] On the other hand, the accumulation of chronic diseases occurs continuously from middle age. A number of recent studies conducted in various countries have reported that the onset of multimorbidity is shifting toward younger age groups.[6, 13-15] However, multimorbidity studies tend to focus on older people, and in-depth knowledge on multimorbidity in younger age groups is lacking.

Here, to evaluate the current status of multimorbidity across age groups and examine its association with clinical outcomes, we analysed a large nationwide medical claims

cohort. Our findings add to existing knowledge by showing that multimorbidity has a significant impact on health starting from middle age and underscore the need for preventive intervention on the public health care level.

Materials and Methods

Data source

We used the nationwide medical claims and enrolment data of the Health Insurance Association for Architecture and Civil Engineering companies (HIA^{2}CE), which is one of the largest social insurance associations in Japan. HIA^{2}CE is a comprehensive insurer which includes 1700 companies, from small engineering companies to middle and large construction companies across Japan. This claims database covers a total of 400 000 insured persons, consisting of employees and their dependents.

The insured-based database is used widely and one of the popular real-world data in Japan.[16] Japan has maintained a universal health coverage system since 1961. All medical information regarding clinical practice covered by this health insurance is included in the medical claims data, except for self-financed medical care and individuals who receive public assistance. Furthermore, medical facilities have been obliged since 2011 to submit medical claims data as an electronic record. Medical claims data include the names of the diagnosed diseases, the names of medical procedures, and the names of prescribed medications, among others. In the present study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and hospitalisations and deaths from the medical claims data in HIA^{2}CE from FY2014 to

FY2018 (April 2014 to March 2019). The enrolment data from HIA^{2}CE includes the medical characteristics and in-out information of insured persons as of April 2019.

Research design and study population

We prepared two data sets for analysis. The first was a cross-sectional data set containing baseline data of FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The study population for this baseline data set included individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since HIA2CE is a type of insurance for workers in Japan, the database include only under 75 years individuals. Therefore, the maximum age in this cohort was 74 years. Participants younger than 20 in FY2014 as well as participants who died during FY2014 were excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to FY2018 (April 2014 to March 2019). The second data set contained participants insured in whole period. We used this cohort data set to conduct Cox regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).

Definition of diagnosed diseases and multimorbidity

There are a variety of definitions for chronic conditions in multimorbidity studies.[17-19] We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the diseases associated with a significant risk of clinical events.[20] The reason, we used CCI, was that we focused on describing the prevalence of each disease and also assessing the association of multimorbidity on hospitalisation or death. The CCI Canadian version has been reported to be applicable to Japanese claims data.[21] We therefore defined diagnosed diseases using medical claims data following ICD-10 codes of the CCI Canada version. We merged the conditions “diabetes with chronic complication” and “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease” and “moderate or severe liver disease” into “liver disease”. The following 15 chronic conditions were included: AIDS/HIV, any malignancy (including lymphoma and leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour, liver disease, myocardial infarction, peptic ulcer disease, renal disease, and rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in the Supplement. Multimorbidity status was defined as the concurrent presence of two or more (≥2) diagnosed diseases among these conditions.[22, 23] We only used confirmed diagnoses, not including suspected diagnoses, in Japanese claims data.

Definition of outcome events; hospitalisation or death

We defined two composite outcomes, hospitalisation or death, which occurred during the period from FY2015 to FY2018. Using the medical claims data, both events were traced by month. In Japan, the validity of death event information is reported to be less sensitive if derived from medical claims data only.[24, 25] Therefore, we also used death information from enrolment data recorded by the insurer: if either contained death information, this was defined as a death event.

Estimation of diagnosed disease prevalence to a nationwide scale

Diagnosed disease prevalence from baseline data was standardised to the nationwide Japanese total population. We calculated prevalence rates according to groups by 5-year age brackets and sex. Then, we estimated the prevalence rates standardized to Japanese total population (age-sex standardized prevalence rate), using the number from the vital statistics 2014 in Japan.[26]

The association of multimorbidity with outcome by age group

To examine the association of multimorbidity with outcome by age group, we performed Cox regression analysis adjusted by sex using cohort data from four consecutive years (FY2015 to FY2018). The independent and additive effect of multimorbidity and aging, we defined combined categories according to three age groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥60, respectively) and the binary status of multimorbidity, with the reference set as no multimorbidity individuals aged 20-39. This model was able to show HR for aging alone (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-39 ages without multimorbidity).

Statistical analysis

Cox regression was conducted for the association of multimorbidity with outcome by age group. Our hypothesis was aging and MM or these combination leads to worsen clinical events. Therefore, we defined six groups which were a combination of 3 categories of generation and MM, and we estimated HR in each group in reference of young (aged 20-39) without MM. Regarding this model, we interpreted both the independent impact of generation and MM on outcomes and the impact of MM in each

generation. Results were considered statistically significant at a two-sided *P*-value of less than 0.05. All analyses were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX, USA).

Patient and Public involvement

Patients or the public were not involved in this research. However, the results of this study will be disseminated to the public through various means including published papers and presentations.

Results

Study participants

We analysed *n* = 246 671 individuals in the baseline data set in FY2014 (Table1) and *n* = 181 959 individuals in the cohort data set FY2014-FY2018. Because the follow-up was four years, the cohort data set was slightly smaller than the baseline data set, especially as a number of young individuals aged 20-24 and older individuals aged >60 dropped out. This may be due to raising children or early retirement, and explains the higher proportion of men in the cohort data set. Mean age and co-morbidity numbers among CCI diseases were mostly comparable between the two data sets, although the prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in disease prevalence between genders were observed. Notably, men had a higher prevalence of diabetes mellitus (P = 0.001) whereas women had a higher prevalence of chronic pulmonary disease (P = 0.002).

Estimated prevalence of multimorbidity in the Japanese total population

The prevalence of diagnosed diseases in FY2014 was applied to the vital statistics of the Japanese population in 2014. The standardised prevalence of multimorbidity was

estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population (eTable 3A in the Supplement). The prevalence rate with age was increased , i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of diseases as well as the below results are shown in eTable 3B in the Supplement). Figure 2B shows the types of diseases and their prevalence across age groups. The top five diseases across the age groups “young” (20-39), “middle-aged (40-59), and “old” (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, and any malignancy; “middle-aged”: chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-44, the top five accelerating diseases were dementia, cerebrovascular disease, peripheral vascular disease, metastatic tumour, and congestive heart failure.

The association of multimorbidity with outcome by age group.

The composite outcomes occurred 17.2% (death 0.8%, hospitalisation 16.9%) in the follow-up period (eTable2). Cox regression analysis showed that young individuals aged 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages ≥60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with multimorbidity has a risk more than ages ≥60 without multimorbidity.

We also assessed HRs for non-multimorbid and multimorbid women and men separately and found that women had a lower HR than men in the 20-39 age group but a higher HR than men in the ≥60 age group (eTable 4 in the Supplement).

Discussion

In this study we analysed nationwide medical claims data for 15 chronic diseases in a large cohort of the general population of Japan. As key findings, standardised prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for women. Further, age group-specific prevalence rates for multimorbidity ranged from 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an accelerating increase after age 40. Importantly, significant differences in the clinical outcomes of multimorbidity versus no multimorbidity were already present in young and middle-aged individuals.

The present study drew individuals covering a wide age range from a nationwide general population. This allowed us to examine the burden of multiple co-morbidities in young, middle-aged and old age groups in the real world. In addition, because Japan has a high medical insurance coverage rate, it was possible to comprehensively identify chronic diseases from receipts. Further, longitudinal analysis enabled us to examine the clinical outcomes of multiple co-morbidities. With regard to limitations, the target population comprised regular employees and their families and might accordingly be healthier than the general population. Also, we defined multimorbidity by disease list included in CCI most likely to lead to death, hence, we were not able to consider other

diseases associated with health-related quality of life loss. CCI originally includes comorbidities that have a strong impact on mortality, not quality of life and well-being. The presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in individuals already suffering from other chronic diseases,[27] younger people,[28] and people with a low socio-economic status.[29] Such diseases often remain undiagnosed or underreported in health records.[30] Also, we collected diseases which were occurred during the year (FY2014). Therefore, patients who were untreated, undiagnosed, or discontinued treatment cannot be picked up. These limitations likely contributed to an underestimation of multimorbidity in our cohort. Further, because we did not manually verify the presence of disease using the physician's medical records data or medication information, disease names extracted from the medical claims data might be incorrect in some cases. In particular, Japanese physicians sometimes change the name of the disease in the medical record to the "correct" disease name for the medication they wish to prescribe, a practice called "disease name for claims data". Because of differences in data sources and study populations, direct comparison of population-based prevalence rates between studies is not straightforward. Nonetheless, the standardised prevalence rates for multimorbidity as reported in the present study - 26.1% for men and 26.0% for women - are similar to those reported by recent studies in

other high-income countries, such as the United States (25% in men, 25% in women), [31] England (24.4% in men, 30% in women), [32] Canada (24.3% whole population),[5] and Denmark (19.3% in men, 23.7% in women).[6] Also recently some Asian countries reported similar prevalence, Iran (13.4% in men, 25.0% in women),[33] India, and Bangladesh (53.7% - 56.5% in both genders, over aged 60).[34] Many previous studies on multimorbidity focused on the older generation, aged 65 and up, because of the larger number of chronic diseases in this age group and the increasing number of people entering it. However, our present data show that already approximately 10% of 30-34-, 19% of 45-49-, and 33% of 55-59-year-olds have ≥2 chronic diseases. Further, 1% of 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥5 chronic diseases. These results show that multimorbidity is already prominent in the middle-aged population. Recent studies reported similar or slightly higher prevalence rates for ≥2 chronic diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)[29] and a Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)[5] population, although these two studies also included mental diseases and osteoporosis, which our present study did not. Our present study shows that, among 15 chronic diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer

disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes mellitus, the prevalence in the present study is similar to that previously reported in an American population (15-30% in individuals aged 55-65)[29] but higher than that in a Canadian population (16.6% in individuals aged 55-64)[4]. The prevalence of chronic pulmonary disease in our present 55-65-year-olds was almost twice as high as those seen for the combined prevalence of asthma and chronic obstructive pulmonary disease (COPD) in an American population aged 55-65 years (5% for men and 10% for women)[29] and in a Canadian population aged 55-64 years (13.7%).[5] This difference might have arisen due to our inclusion of various other pulmonary diseases besides asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in the present study was comparable to that seen in an adult population in Northern Italy[35] and in an adult population in Korea,[36] although this comparison requires care since the types of liver disease in these studies and the age groups included vary.

Analysis of clinical outcomes using Cox regression revealed that the presence of multimorbidity increased HRs in all age groups, including young individuals. In addition, the comparison of the increased HRs resulting from multimorbidity versus no multimorbidity showed that the impact of multimorbidity exceeds that of increasing age. These results indicate that multimorbidity places a burden on all age groups.

The five most prevalent diseases (diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease, and any malignancy) in the present study are lifestyle-related diseases that develop slowly over time. This trend should be greeted with alarm. We trust that this study raises awareness of the potential health risks and burden associated with the early onset of multimorbidity in young and middle-aged, the period when one is busy working and raising children. Future studies should investigate the specific lifestyle factors associated with an elevated risk of multimorbidity in the Japanese working population. Ultimately, public health care policies should be aimed at efforts to reverse the trend toward early multimorbidity onset.

In conclusion, the present study confirmed the prevalence of MM by including in the denominator those who did not have the receipt of medical claims and to estimate the prevalence of MM in the general population. Furthermore, we revealed that the impact of multimorbidity is already clinically significant in middle-aged Japanese, with elevated adverse events such as hospitalisation or death. In addition, the risk posed by multimorbidity exceeds that of aging in all age groups. These results underscore the need to undertake healthcare intervention against the onset of multimorbidity before middle-aged, and not to leave it as a problem for geriatricians.

Ethical Approval

The present study was approved by the Institutional Review Board (IRB) of Kyoto University (approval number: R0817). All data were anonymised before analysis and none of the researchers had access to patient-identifiable information. The IRB waived informed consent for this observational study.

Data Availability Statement

All data are incorporated into the article and its online supplementary material.

Author Contributions

Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS. Administrative, technical, or material support: YS, SF. Study supervision: SF, AI, TN. YS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval and agreed to be accountable for all aspects of work.

Acknowledgements

The authors are grateful to HIA^{2}CE for providing data for the present study.

Funding

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in the design of the study; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Competing Interests

None declared.

Patient Consent for Publication

Not applicable.

Figure Legends

Figure 1. Participant selection flowchart. FY; fiscal year

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A**) Percentage of the population having 0 to ≥5 chronic diseases by age group. **B**) Prevalence of the top ten chronic diseases by age group. **C**) The top ten chronic diseases with the steepest increase after age 40-44 years.

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

References

1 Bleich SN, Sherrod C, Chiang A*, et al*. Systematic Review of Programs Treating High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities in the United States, 2008-2014. *Prev Chronic Dis*. Nov 12 2015;12:E197. doi:10.5888/pcd12.150275

2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. *Prev Med Rep*. Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008

3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y, Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of

multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614. doi:10.1371/journal.pone.0243614

4 Low LL, Kwan YH, Ko MSM*, et al*. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245. doi:10.1001/jamanetworkopen.2019.15245

5 Pefoyo AJ, Bronskill SE, Gruneir A*, et al*. The increasing burden and complexity of multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-1733-2

6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the prevalence of multimorbidity - A register-based population study. *BMC Public Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8

7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of multimorbidity on healthcare utilisation and work productivity by socioeconomic groups: Cross-sectional analyses of Australia and Japan. *PLoS One*. 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281

8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. *BMC Health Serv Res*. Jan 22 2015;15:23. doi:10.1186/s12913-015-0698-2

9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-

sectional study based on nationwide claims data. *BMJ Open*. Jun 9 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333

10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812. doi:10.1136/bmjopen-2016-012812

11 Picco L, Achilla E, Abdin E*, et al*. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10 2016;16:173. doi:10.1186/s12913-016-1421-7

12 van den Bussche H, Schon G, Kolonko T*, et al*. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity--results from a claims data based observational study in Germany. *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54

13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152. doi:10.1186/s12916-017-0913-6

14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising burden of multimorbidity and related socio-demographic factors: a repeated cross-sectional study of Ontarians. *Can J Public Health*. Apr 13 2021;doi:10.17269/s41997-021-00474-y

15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the

ageing population of England, 2002-2015. *J Comorb*. Jan-Dec 2019;9:2235042X19872030. doi:10.1177/2235042X19872030

16 Katsutoshi H, Annabel B, Yasuhiko M, et al. Current Status, Challenges, and Future Perspectives of Real-World Data and Real-World Evidence in Japan. *Drugs - Real World Outcomes.* 2021;8:459–480. doi:org/10.1007/s40801-021-00266-3

17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments used for measuring the association of the level of multimorbidity and clinically important outcomes. *BMJ Open*. 2021;May 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.

18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.

19 Jürisson M, Heti P, Anneli U, et al. Prevalence of chronic conditions and multimorbidity in Estonia: a population-based cross-sectional study. *BMJ Open.* 2021;Oct 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.

20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan H, Li B, Couris CM*, et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*. 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.

22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*. Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098

23 Le Reste JY, Nabbe P, Manceau B*, et al*. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001

24 Ooba N, Setoguchi S, Ando T*, et al*. Claims-based definition of death in Japanese claims database: validity and implications. *PLoS One*. 2013;8(5):e66116. doi:10.1371/journal.pone.0066116

25 Sakai M, Ohtera S, Iwao T*, et al*. Validation of claims data to identify death among aged persons utilizing enrollment data from health insurance unions. *Environ Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3

26 Statistics Bureau of Japan. Preliminary count of the Japanese population. Accessed March, 2014. http://www.stat.go.jp/data/jinsui/index.html

27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234

28 Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost

productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002

29 Rocca WA, Boyd CM, Grossardt BR*, et al*. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49. doi:10.1016/j.mayocp.2014.07.010

30 Cassell A, Edwards D, Harshfield A*, et al*. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. Apr 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465

31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E*, et al*. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251

32 St Sauver JL, Boyd CM, Grossardt BR*, et al*. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413

33 Masoomeh A, Azam M, Mehdi Y. et al. Multimorbidity as an important issue among women: results of a gender difference investigation in a large population-based cross-sectional study in West Asia. *BMJ Open*. 2017;May 9;7(5):e013548. doi: 10.1136/bmjopen-2016-013548.

34 Sanghamitra P, Subhashisa S, Mohammad AH, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review bmj open. *BMJ Open*. 2015 Oct 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.

35 Bellentani S, Tiribelli C, Saccoccio G*, et al*. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec 1994;20(6):1442-9. doi:10.1002/hep.1840200611

36 Park SH, Plank LD, Suk KT*, et al*. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr 2020;26(2):209-215. doi:10.3350/cmh.2019.0065

Supplementary Information

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population

	Baseline data in FY2014					
	Overall		**Men**		**Women**	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%
Men	144,237	58.5	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8
20-24	18,524	7.5	11,315	7.8	7,209	7.0
25-29	17,251	7.0	12,014	8.3	5,237	5.1
30-34	18,093	7.3	11,104	7.7	6,989	6.8
35-39	23,878	9.7	13,278	9.2	10,600	0.3
40-44	39,721	16.1	21,640	15.0	18,081	17.7
45-49	40,908	16.6	24,191	16.8	16,717	16.3
50-54	29,466	11.9	17,577	12.2	11,889	11.6
55-59	20,149	8.2	11,343	7.9	8,806	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4
65-69	11,931	4.8	6,768	4.7	5,163	5.0
70-74	5,472	2.2	2,301	1.6	3,171	3.1
AIDS/HIV	96	0.0	62	0.0	34	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9
Dementia	447	0.2	210	0.1	237	0.2
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6
Renal disease	2,573	1.0	1,751	1.2	822	0.8
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3
Disease no. among CCI						
no disease	171,140	69.4	101,857	70.6	69,283	67.6
1 disease	22,947	9.3	12,032	8.3	10,915	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7
Multimorbidity (≥2 diseases among CCI)	52,584	21.3	30,348	21.0	22,236	21.7

Values are numbers (%) unless otherwise stated.
[a] Any malignancy includes leukemia and lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

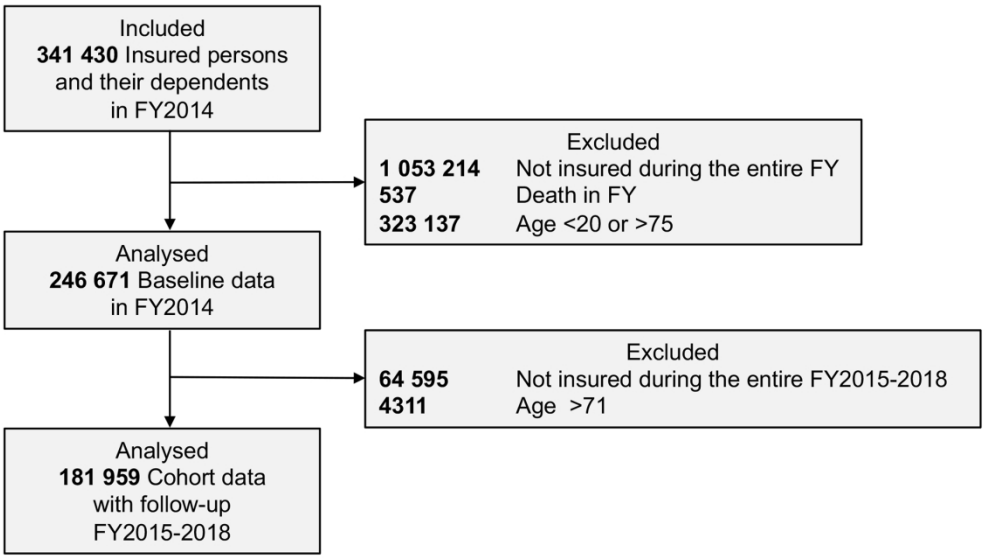

Figure 1. Participant selection flowchart. FY; fiscal year

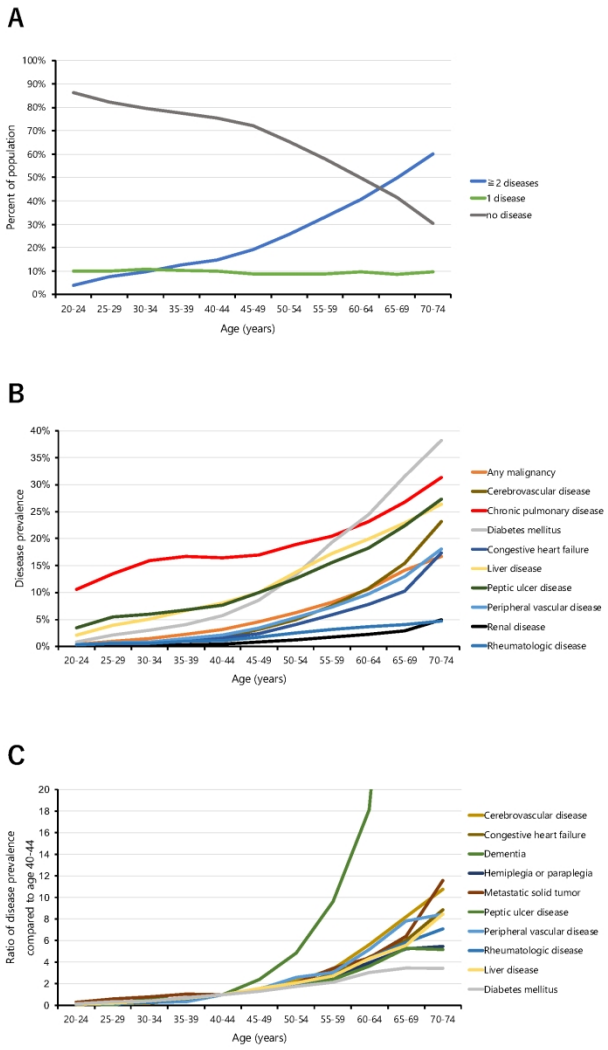

Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥5 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44 years.

297x420mm (200 x 200 DPI)

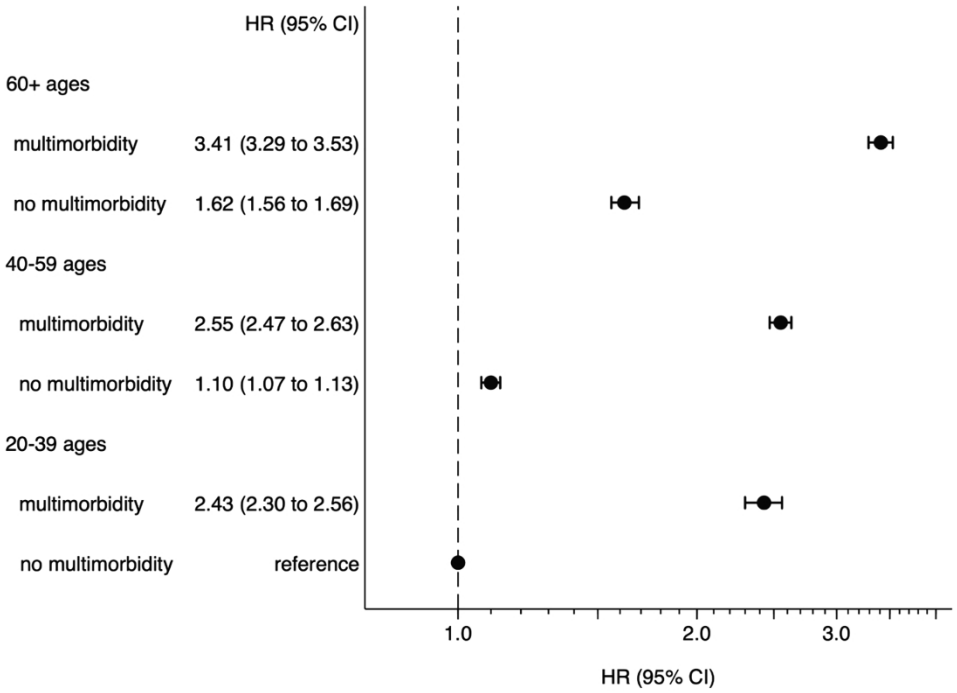

Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥2 diagnosed diseases) in three age groups in a 5-year cohort of *n* = 181 959 Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

Supplementary material

Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation

Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

Supplementary eTable 3A. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by gender

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Supplementary eTable 1. List of diseases and their ICD-10 codes used to define diseases in medical claims data

Diseases	ICD-10 codes
AIDS/HIV	B20.x-B22.x, B24.x
Any malignancy, incl. leukemia and lymphoma	C00.x-C26.x, C30.x-C34.x, C37.x-C41x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.3, C88.7, C88.9, C90.0, C90.1, C91.x- C93.x, C94.0-C94.3, C94.5, C94.7, C95.x, C96.x, C43.x, C88.0-C88.2, C90.2, C94.4, C97.x
Cerebrovascular disease	I69.x, G45.x, G46.x, H34.0, I60.x-I68.x
Chronic pulmonary disease	J41.x-J47.x, J60.x-J66.x, I27.8, I27.9, J40.x, J67.x, J68.4, J70.1, J70.3
Congestive heart failure	I50.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5- I42.9, I43.x, P29.0
Dementia	F00.x-F02.x, F03.x, F05.1, G30.x, G31.1
Diabetes with chronic complication	E10.2-E10.4, E11.2-E11.4, E13.2-E13.4, E14.2-E14.4, E10.5, E10.7, E11.5, E11.7, E12.2-E12.5, E12.7, E13.5, E13.7, E14.5, E14.7
Diabetes without chronic complication	E10.1, E10.9, E11.1, E11.9, E13.1, E13.9, E14.1, E14.9, E10.0, E10.6, E10.8, E11.0, E11.6, E11.8, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.6, E13.8, E14.0, E14.6, E14.8
Hemiplegia or paraplegia	G81.x, G82.0-G82.2, G04.1, G11.4, G80.1, G80.2, G82.3-G82.5, G83.0-G83.4, G83.9
Metastatic solid tumor	C77.x-C79.x, C80.x
Mild liver disease	K70.3, K71.7, K73.x, K74.3- K74.6, B18.x, K70.0-K70.2, K70.9, K71.3-K71.5, K74.0-K74.2, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	K72.1, K72.9, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K76.5
Myocardial infarction	I25.2, I21.x, I22.x
Peptic ulcer disease	K25.4-K25.7, K26.4-K26.7, K27.4-K27.7, K28.4-K28.7, K25.0-K25.3, K25.9, K26.0-K26.3, K26.9, K27.0-K27.3, K27.9, K28.0-K28.3, K28.9
Peripheral vascular disease	I71.x, I73.9, Z95.8, Z95.9, I70.x, I73.1, I73.8, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9

Renal disease	N18.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Rheumatology disease	M05.x, M06.0, M32.x, M33.2, M34.x, M35.3, M06.1-M06.4, M06.8, M06.9, M31.5, M33.0, M33.1, M33.9, M35.1, M36.0

Supplementary eTable 2. Characteristics of baseline data in fiscal year 2014 and cohort data

	Baseline data in FY2014		Cohort data		*P*-value[c]
N	242,360	(100%)	181,959	(100%)	
Men	142,471	(58.8%)	111,088	(61.1%)	<0.01
Age (Mean, SD)	44.5	(12.5)	44.7	(10.6)	<0.01
20-24	18,524	(7.6%)	5,052	(2.8%)	<0.01
25-29	17,251	(7.1%)	12,675	(7.0%)	
30-34	18,093	(7.5%)	14,784	(8.1%)	
35-39	23,878	(9.9%)	20,508	(11.3%)	
40-44	39,721	(16.4%)	35,168	(19.3%)	
45-49	40,908	(16.9%)	37,124	(20.4%)	
50-54	29,466	(12.2%)	25,906	(14.2%)	
55-59	20,149	(8.3%)	13,052	(7.2%)	
60-64	21,278	(8.8%)	10,735	(5.9%)	
65-69	11,931	(4.9%)	6,246	(3.4%)	
70-71	1,161	(0.5%)	709	(0.4%)	
AIDS/HIV	94	(0.0%)	74	(0.0%)	0.76
Any malignancy[a]	11,343	(4.7%)	8,377	(4.6%)	0.24
Cerebrovascular disease	9,860	(4.1%)	6,971	(3.8%)	<0.01
Chronic pulmonary disease	41,866	(17.3%)	32,093	(17.6%)	<0.01
Congestive heart failure	7,751	(3.2%)	5,710	(3.1%)	0.27
Dementia	291	(0.1%)	190	(0.1%)	0.13
Diabetes mellitus	25,716	(10.6%)	18,755	(10.3%)	<0.01
Hemiplegia or paraplegia	729	(0.3%)	507	(0.3%)	0.19

Liver disease	25,999	(10.7%)	19,725	(10.8%)	0.24
Metastatic solid tumor	2,381	(1.0%)	1,823	(1.0%)	0.53
Myocardial infarction	1,526	(0.6%)	1,092	(0.6%)	0.22
Peptic ulcer disease	24,859	(10.3%)	18,594	(10.2%)	0.68
Peripheral vascular disease	9,623	(4.0%)	7,083	(3.9%)	0.20
	Baseline data in FY2014		**Cohort data**		***P*-value[c]**
N	242,360	(100%)	181,959	(100%)	
Renal disease	2,350	(1.0%)	1,747	(1.0%)	0.75
Rheumatologic disease	3,931	(1.6%)	2,926	(1.6%)	0.72
At least one disease among the top five[b]	69,014	(28.5%)	50,660	(27.8%)	<0.01
Disease no. among CCI (Mean, SD)	0.8	(1.6)	0.8	(1.6)	0.16
0 disease	169,872	(70.1%)	129,037	(70.9%)	<0.01
1 disease	22,514	(9.3%)	15,532	(8.5%)	
2 diseases	16,605	(6.9%)	12,375	(6.8%)	
3 diseases	12,242	(5.1%)	9,046	(5.0%)	
4 diseases	9,076	(3.7%)	6,816	(3.7%)	
≥ 5 diseases	12,051	(5.0%)	9,153	(5.0%)	
Multimorbidity (≥2 diseases among CCI)	49,974	(20.6%)	37,390	(20.5%)	
Composite outcomes	36,893	(15.2%)	31,224	(17.2%)	<0.01
Death	1,507	(0.6%)	1,507	(0.8%)	
Hospitalisation	36,495	(15.1%)	30,826	(16.9%)	

[a] Any malignancy includes leukemia and lymphoma.

[b] Top 5 diseases include chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and cerebrovascular disease.

SD; standard deviation, CCI; Charlson Comorbidity Index

[c] Age (Mean) and Co-morbidity no. (Mean): Student`s t-test. All other variables: Pearson's chi-square test.

Supplementary eTable 3A. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population by gender

	Baseline data in FY2014						Japanese total population					
	Overall		Men		Women		Overall		Men		Women	
	N=246,671	%	*N*=144,237	%	*N*=102,434	%	*N*=88,923,000	%	*N*=44,288,000	%	*N*=44,640,000	%
Men	144,237	58.5	-	-	-	-	44,288,000	49.8	-	-	-	-
Age (Mean, SD)	45.0	12.9	44.6	12.9	45.7	12.8	48.0	15.3	47.7	15.3	48.4	15.4
20-24	18,524	7.5	11,315	7.8	7,209	7.0	6,203,000	7.0	3,192,000	7.2	3,012,000	6.7
25-29	17,251	7.0	12,014	8.3	5,237	5.1	6,677,000	7.5	3,414,000	7.7	3,264,000	7.3
30-34	18,093	7.3	11,104	7.7	6,989	6.8	7,466,000	8.4	3,788,000	8.6	3,680,000	8.2
35-39	23,878	9.7	13,278	9.2	10,600	0.3	8,670,000	9.8	4,394,000	9.9	4,276,000	9.6
40-44	39,721	16.1	21,640	15.0	18,081	17.7	9,793,000	11.0	4,956,000	11.2	4,837,000	10.8
45-49	40,908	16.6	24,191	16.8	16,717	16.3	8,609,000	9.7	4,329,000	9.8	4,278,000	9.6
50-54	29,466	11.9	17,577	12.2	11,889	11.6	7,790,000	8.8	3,903,000	8.8	3,887,000	8.7
55-59	20,149	8.2	11,343	7.9	8,806	8.6	7,653,000	8.6	3,802,000	8.6	3,853,000	8.6
60-64	21,278	8.6	12,706	8.8	8,572	8.4	8,979,000	0.1	4,406,000	9.9	4,573,000	10.2
65-69	11,931	4.8	6,768	4.7	5,163	5.0	9,155,000	10.3	4,414,000	10.0	4,741,000	10.6
70-74	5,472	2.2	2,301	1.6	3,171	3.1	7,928,000	8.9	3,690,000	8.3	4,239,000	9.5
AIDS/ HIV	96	0.0	62	0.0	34	0.0	34,034	0.0	18,979	0.0	15,055	0.0
Any malignancy[a]	12,047	4.9	5,611	3.9	6,436	6.3	5,775,260	6.5	2,668,349	6.0	3,106,911	7.0
Cerebrovascular disease	10,866	4.4	6,510	4.5	4,356	4.3	5,773,295	6.5	3,023,765	6.8	2,749,530	6.2
Chronic pulmonary disease	43,216	17.5	22,484	15.6	20,732	20.2	17,303,735	19.5	7,713,864	17.4	9,589,871	21.5
Congestive heart failure	8,497	3.4	5,515	3.8	2,982	2.9	4,317,076	4.9	2,459,170	5.6	1,857,906	4.2
Dementia	447	0.2	210	0.1	237	0.2	410,326	0.5	179,350	0.4	230,976	0.5
Diabetes mellitus	27,344	11.1	17,881	12.4	9,463	9.2	12,689,040	14.3	7,122,240	16.1	5,566,801	12.5
Hemiplegia or paraplegia	813	0.3	533	0.4	280	0.3	424,609	0.5	253,040	0.6	171,569	0.4
Liver disease	27,127	11.0	16,954	11.8	10,173	9.9	11,341,444	2.8	6,031,029	13.6	5,310,415	11.9
Metastatic solid tumor	2,532	1.0	1,263	0.9	1,269	1.2	1,235,336	1.4	598,734	1.4	636,601	1.4
Myocardial infarction	1,628	0.7	1,325	0.9	303	0.3	769,977	0.9	575,894	1.3	194,083	0.4
Peptic ulcer disease	26,047	10.6	14,511	10.1	11,536	11.3	11,238,524	12.6	5,485,994	12.4	5,752,530	12.9
Peripheral vascular disease	10,407	4.2	5,723	4.0	4,684	4.6	5,197,644	5.8	2,503,359	5.7	2,694,285	6.0
Renal disease	2,573	1.0	1,751	1.2	822	0.8	1,261,138	1.4	784,770	1.8	476,367	1.1
Rheumatologic disease	4,146	1.7	1,397	1.0	2,749	2.7	1,928,685	2.2	530,072	1.2	1,398,613	3.1
≥1 disease among top 5	71,880	29.1	40,833	28.3	31,047	30.3	30,041,150	33.8	14,676,045	33.1	15,365,106	34.4
Disease no. among CCI												
no disease	171,140	69.4	101,857	70.6	69,283	67.6	57,293,691	64.4	29,006,814	65.5	28,286,877	63.4
1 disease	22,947	9.3	12,032	8.3	10,915	10.7	8,464,436	9.5	3,702,220	8.4	4,762,216	10.7
2 diseases	17,120	6.9	8,994	6.2	8,126	7.9	6,799,080	7.6	3,029,535	6.8	3,769,544	8.4
3 diseases	12,822	5.2	7,273	5.0	5,549	5.4	5,534,827	6.2	2,652,231	6.0	2,882,596	6.5
4 diseases	9,588	3.9	5,874	4.1	3,714	3.6	4,261,753	4.8	2,242,062	5.1	2,019,691	4.5
≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7	6,574,213	7.4	3,655,138	8.3	2,919,075	6.5
Multimorbidity	52,584	21.3	30,348	21.0	22,236	21.7	23,169,873	26.1	11,578,966	26.1	11,590,906	26.0

(≥2 diseases among CCI)

Values are numbers (%) unless otherwise

[a] Any malignancy includes leukemia and lymphoma.

FY; fiscal year

SD; standard deviation

CCI; Charlson Comorbidity Index

Supplementary eTable 3B. Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		20-24		25-29		30-34	
	88,923,000	(100%)	6,204,000	(100%)	6,678,000	(100%)	7,468,000	(100%)
Men	44,288,000	(49.8%)	3,192,000	(51.5%)	3,414,000	(51.1%)	3,788,000	(50.7%)
AIDS/HIV	34,034	(0.0%)	1,400	(0.0%)	1,137	(0.0%)	1,394	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	24,047	(0.4%)	60,604	(0.9%)	103,907	(1.4%)
Cerebrovascular disease	5,773,295	(6.5%)	12,484	(0.2%)	23,767	(0.4%)	40,440	(0.5%)
Chronic pulmonary disease	17,303,735	(19.5%)	656,012	(10.6%)	901,156	(13.5%)	1,184,702	(15.9%)
Congestive heart failure	4,317,076	(4.9%)	21,322	(0.3%)	34,950	(0.5%)	52,469	(0.7%)
Dementia	410,326	(0.5%)	418	(0.0%)	0	(0.0%)	1,053	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	50,290	(0.8%)	141,852	(2.1%)	228,348	(3.1%)
Hemiplegia or paraplegia	424,609	(0.5%)	3,782	(0.1%)	7,489	(0.1%)	10,227	(0.1%)
Liver disease	11,341,444	(12.8%)	129,091	(2.1%)	259,190	(3.9%)	380,993	(5.1%)
Metastatic solid tumor	1,235,336	(1.4%)	6,706	(0.1%)	9,643	(0.1%)	15,804	(0.2%)
Myocardial infarction	769,977	(0.9%)	3,510	(0.1%)	3,859	(0.1%)	7,438	(0.1%)
Peptic ulcer disease	11,238,524	(12.6%)	213,860	(3.4%)	364,164	(5.5%)	444,445	(6.0%)
Peripheral vascular disease	5,197,644	(5.8%)	20,276	(0.3%)	42,759	(0.6%)	60,055	(0.8%)
Renal disease	1,261,138	(1.4%)	6,164	(0.1%)	11,118	(0.2%)	19,957	(0.3%)
Rheumatologic disease	1,928,685	(2.2%)	17,602	(0.3%)	35,051	(0.5%)	43,777	(0.6%)
no disease	57,293,691	(64.4%)	5,352,990	(86.3%)	5,500,039	(82.4%)	5,935,225	(79.5%)
1 disease	8,464,436	(9.5%)	609,768	(9.8%)	666,087	(10.0%)	805,022	(10.8%)
2 diseases	6,799,080	(7.6%)	163,269	(2.6%)	310,407	(4.6%)	399,222	(5.3%)
3 diseases	5,534,827	(6.2%)	45,066	(0.7%)	104,758	(1.6%)	178,423	(2.4%)
4 diseases	4,261,753	(4.8%)	19,190	(0.3%)	52,301	(0.8%)	77,876	(1.0%)
≥ 5 diseases	6,574,213	(7.4%)	13,716	(0.2%)	44,409	(0.7%)	72,233	(1.0%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	241,241	(3.9%)	511,875	(7.7%)	727,754	(9.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		35-39		40-44		45-49	
	88,923,000	(100%)	8,670,000	(100%)	9,793,000	(100%)	8,607,000	(100%)
Men	44,288,000	(49.8%)	4,394,000	(50.7%)	4,956,000	(50.6%)	4,329,000	(50.3%)
AIDS/HIV	34,034	(0.0%)	4,592	(0.1%)	4,124	(0.0%)	3,069	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	198,069	(2.3%)	308,591	(3.2%)	393,299	(4.6%)
Cerebrovascular disease	5,773,295	(6.5%)	93,413	(1.1%)	170,645	(1.7%)	265,098	(3.1%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,446,109	(16.7%)	1,613,639	(16.5%)	1,462,084	(17.0%)
Congestive heart failure	4,317,076	(4.9%)	90,394	(1.0%)	155,193	(1.6%)	201,862	(2.3%)
Dementia	410,326	(0.5%)	734	(0.0%)	1,490	(0.0%)	3,606	(0.0%)
Diabetes mellitus	12,689,040	(14.3%)	352,333	(4.1%)	553,455	(5.7%)	737,731	(8.6%)
Hemiplegia or paraplegia	424,609	(0.5%)	13,621	(0.2%)	12,793	(0.1%)	19,669	(0.2%)
Liver disease	11,341,444	(12.8%)	577,316	(6.7%)	784,095	(8.0%)	858,769	(10.0%)
Metastatic solid tumor	1,235,336	(1.4%)	29,912	(0.3%)	56,656	(0.6%)	78,055	(0.9%)
Myocardial infarction	769,977	(0.9%)	8,925	(0.1%)	25,198	(0.3%)	37,793	(0.4%)
Peptic ulcer disease	11,238,524	(12.6%)	589,633	(6.8%)	749,581	(7.7%)	856,494	(10.0%)
Peripheral vascular disease	5,197,644	(5.8%)	127,339	(1.5%)	201,866	(2.1%)	288,167	(3.3%)
Renal disease	1,261,138	(1.4%)	30,634	(0.4%)	46,209	(0.5%)	73,397	(0.9%)
Rheumatologic disease	1,928,685	(2.2%)	79,300	(0.9%)	108,081	(1.1%)	143,756	(1.7%)
no disease	57,293,691	(64.4%)	6,707,086	(77.4%)	7,389,249	(75.5%)	6,205,507	(72.1%)
1 disease	8,464,436	(9.5%)	879,686	(10.1%)	969,263	(9.9%)	762,446	(8.9%)
2 diseases	6,799,080	(7.6%)	529,075	(6.1%)	633,182	(6.5%)	588,650	(6.8%)
3 diseases	5,534,827	(6.2%)	284,566	(3.3%)	352,334	(3.6%)	416,546	(4.8%)
4 diseases	4,261,753	(4.8%)	152,965	(1.8%)	232,087	(2.4%)	297,143	(3.5%)
≥ 5 diseases	6,574,213	(7.4%)	116,621	(1.3%)	216,885	(2.2%)	336,707	(3.9%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	1,083,227	(12.5%)	1,434,488	(14.6%)	1,639,046	(19.0%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		50-54		55-59		60-64	
	88,923,000	(100%)	7,790,000	(100%)	7,655,000	(100%)	8,979,000	(100%)
Men	44,288,000	(49.8%)	3,903,000	(50.1%)	3,802,000	(49.7%)	4,406,000	(49.1%)
AIDS/HIV	34,034	(0.0%)	2,979	(0.0%)	3,324	(0.0%)	5,281	(0.1%)
Any malignancy[a]	5,775,260	(6.5%)	483,592	(6.2%)	624,101	(8.2%)	958,696	(10.7%)
Cerebrovascular disease	5,773,295	(6.5%)	387,663	(5.0%)	573,513	(7.5%)	965,151	(10.7%)
Chronic pulmonary disease	17,303,735	(19.5%)	1,469,169	(18.9%)	1,565,078	(20.4%)	2,074,822	(23.1%)
Congestive heart failure	4,317,076	(4.9%)	316,491	(4.1%)	443,956	(5.8%)	694,542	(7.7%)
Dementia	410,326	(0.5%)	7,254	(0.1%)	14,375	(0.2%)	27,048	(0.3%)
Diabetes mellitus	12,689,040	(14.3%)	1,028,899	(13.2%)	1,477,049	(19.3%)	2,197,472	(24.5%)
Hemiplegia or paraplegia	424,609	(0.5%)	26,826	(0.3%)	43,702	(0.6%)	56,416	(0.6%)
Liver disease	11,341,444	(12.8%)	1,063,948	(13.7%)	1,316,086	(17.2%)	1,785,515	(19.9%)
Metastatic solid tumor	1,235,336	(1.4%)	104,654	(1.3%)	136,279	(1.8%)	204,377	(2.3%)
Myocardial infarction	769,977	(0.9%)	65,457	(0.8%)	76,970	(1.0%)	130,757	(1.5%)
Peptic ulcer disease	11,238,524	(12.6%)	977,192	(12.5%)	1,190,533	(15.6%)	1,633,285	(18.2%)
Peripheral vascular disease	5,197,644	(5.8%)	411,839	(5.3%)	554,776	(7.2%)	876,673	(9.8%)
Renal disease	1,261,138	(1.4%)	95,578	(1.2%)	126,432	(1.7%)	202,057	(2.3%)
Rheumatologic disease	1,928,685	(2.2%)	191,910	(2.5%)	235,332	(3.1%)	326,918	(3.6%)
no disease	57,293,691	(64.4%)	5,087,646	(65.3%)	4,435,684	(57.9%)	4,468,987	(49.8%)
1 disease	8,464,436	(9.5%)	687,805	(8.8%)	680,727	(8.9%)	859,388	(9.6%)
2 diseases	6,799,080	(7.6%)	631,794	(8.1%)	687,732	(9.0%)	933,542	(10.4%)
3 diseases	5,534,827	(6.2%)	510,570	(6.6%)	638,438	(8.3%)	881,741	(9.8%)
4 diseases	4,261,753	(4.8%)	382,265	(4.9%)	509,123	(6.7%)	729,058	(8.1%)
≥ 5 diseases	6,574,213	(7.4%)	489,921	(6.3%)	703,297	(9.2%)	1,106,284	(12.3%)

Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	2,014,550	(25.9%)	2,538,590	(33.2%)	3,650,625	(40.7%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 3. (continued) Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by age group

	Overall		65-69		70-74	
	88,923,000	(100%)	9,155,000	(100%)	7,929,000	(100%)
Men	44,288,000	(49.8%)	4,414,000	(48.2%)	3,690,000	(46.5%)
AIDS/HIV	34,034	(0.0%)	3,793	(0.0%)	2,940	(0.0%)
Any malignancy[a]	5,775,260	(6.5%)	1,296,908	(14.2%)	1,323,445	(16.7%)
Cerebrovascular disease	5,773,295	(6.5%)	1,404,663	(15.3%)	1,836,456	(23.2%)
Chronic pulmonary disease	17,303,735	(19.5%)	2,445,425	(26.7%)	2,485,540	(31.3%)
Congestive heart failure	4,317,076	(4.9%)	931,107	(10.2%)	1,374,790	(17.3%)
Dementia	410,326	(0.5%)	83,286	(0.9%)	271,063	(3.4%)
Diabetes mellitus	12,689,040	(14.3%)	2,891,848	(31.6%)	3,029,762	(38.2%)
Hemiplegia or paraplegia	424,609	(0.5%)	81,998	(0.9%)	148,087	(1.9%)
Liver disease	11,341,444	(12.8%)	2,094,406	(22.9%)	2,092,035	(26.4%)
Metastatic solid tumor	1,235,336	(1.4%)	300,280	(3.3%)	292,970	(3.7%)
Myocardial infarction	769,977	(0.9%)	197,033	(2.2%)	213,037	(2.7%)
Peptic ulcer disease	11,238,524	(12.6%)	2,053,538	(22.4%)	2,165,800	(27.3%)
Peripheral vascular disease	5,197,644	(5.8%)	1,181,335	(12.9%)	1,432,557	(18.1%)
Renal disease	1,261,138	(1.4%)	257,988	(2.8%)	391,604	(4.9%)
Rheumatologic disease	1,928,685	(2.2%)	374,826	(4.1%)	372,134	(4.7%)
no disease	57,293,691	(64.4%)	3,803,485	(41.5%)	2,407,794	(30.4%)
1 disease	8,464,436	(9.5%)	785,842	(8.6%)	758,403	(9.6%)
2 diseases	6,799,080	(7.6%)	1,013,307	(11.1%)	908,900	(11.5%)
3 diseases	5,534,827	(6.2%)	1,074,487	(11.7%)	1,047,899	(13.2%)
4 diseases	4,261,753	(4.8%)	886,159	(9.7%)	923,584	(11.6%)

≥ 5 diseases	6,574,213	(7.4%)	1,591,721	(17.4%)	1,882,418	(23.7%)
Multimorbidity (≥2 diseases among CCI)	23,169,873	(26.1%)	4,565,674	(49.9%)	4,762,801	(60.1%)

[a]Any malignancy includes leukemia and lymphoma.

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Overall[a]												
	Full Model			**20-39 years**			**40-59 years**			**60-71 years**		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	1.02	1.01	1.02									
Sex	0.97	0.95	0.99	0.36	0.34	0.37	1.29	1.25	1.33	1.44	1.38	1.51
≥2 diseases	2.17	2.12	2.21	2.17	2.05	2.29	2.31	2.24	2.38	2.05	1.97	2.14
Men[b]												
Age	1.03	1.03	1.04									
≥2 diseases	2.04	1.98	2.10	2.81	2.56	3.07	2.25	2.17	2.34	1.94	1.84	2.04
Women[b]												
Age	0.99	0.99	1.00									
≥2 diseases	2.22	2.15	2.30	1.91	1.78	2.04	2.42	2.30	2.54	2.28	2.12	2.44

[a]References are female for sex, no disease for morbidity variables

[b]Reference is no disease for morbidity variables

HR; hazard ratio, CI; confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig. 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl. Table 2
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1, Suppl. Tables 3-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, Fig. 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, Fig. 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.