

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **1 Title**

5
6
7 2 The burden of multimorbidity across generations in Japan 2014-2019 - a historical
8
9
10 3 cohort study using nationwide medical claims data
11
12

13 4
14
15
16 **5 Authors**

17
18
19 6 Yoshiyuki Saito^{1,2*} PharmD, Ataru Igarashi^{1,3} PhD, Takeo Nakayama² MD PhD, Shingo
20
21
22 7 Fukuma⁴ MD
23
24

25 8
26
27
28 **9 Author Affiliations**

29
30
31 10 ¹Department of Health Economics & Outcomes Research, Graduate School of
32
33
34 11 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo
35
36
37 12 113-0033, Japan

38
39
40 13 ²Department of Health Informatics, School of Public Health, Graduate School of
41
42
43 14 Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

44
45
46 15 ³Unit of Public Health and Preventive Medicine, Yokohama City University School of
47
48
49 16 Medicine, Kanagawa 236-0027, Japan

50
51
52 17 ⁴School of Human Health Sciences, Graduate School of Medicine, Kyoto University,
53
54
55 18 Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan
56
57
58
59
60

1
2
3
4 195
6
7 20 **Running head**8
9
10 21 The burden of multimorbidity in Japan 2014-201911
12
13 2214
15
16 23 ***Corresponding author**17
18
19 24 Yoshiyuki Saito, PharmD20
21
22 25 Department of Health Economics & Outcomes Research, Graduate School of23
24
25 26 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo26
27
28 27 113-0033, Japan29
30
31 28 E-mail: saito.yoshiyuki.86x@kyoto-u.jp32
33
34 29 Tel: +81-3-5841-482835
36
37 3038
39
40 31 Word count: 3121 (incl. abstract)41
42
43 32 Tables: 144
45
46 33 Figures: 347
48
49 34 Supplementary Tables: 450
51
52 3553
54
55 36

1
2
3
4 37 **Abstract**

5
6
7 38 **Objective**

8
9
10 39 To describe the prevalence of multimorbidity and its associations with clinical outcomes
11
12
13 40 across age groups.

14
15
16 41 **Design**

17
18
19 42 Historical cohort study using nationwide medical claims data.

20
21
22 43 **Setting**

23
24
25 44 Carried out in Japan between April 2014 and March 2019.

26
27
28 45 **Participants**

29
30
31 46 N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance
32
33
34 47 Association for Architecture and Civil Engineering companies (HIA²CE) were included
35
36
37 48 into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals
38
39
40 49 were included into the cohort data set spanning FY2014-FY2018.

41
42
43 50 **Exposures**

44
45
46 51 Multimorbidity was defined as having ≥ 2 of 15 chronic conditions according to the ICD-
47
48
49 52 10 codes of the Charlson Comorbidity Index.

50
51
52 53 **Primary and Secondary Outcomes**

1
2
3
4 54 Primary outcome: The standardised prevalence of multimorbidity across age groups
5
6
7 55 was evaluated using data from FY 2014 and extrapolated to the Japanese total
8
9
10 56 population. Secondary Outcome: Hospitalisation and death events were traced by
11
12
13 57 month using medical claims data and insurer enrolment data. Associations between
14
15
16 58 multimorbidity and 5-year hospitalisation and/or death events across age groups were
17
18
19 59 analysed using a Cox regression model.
20
21

22 60 **Results**

23
24
25 61 The standardised prevalence of multimorbidity was approximately 5% (ages 20-29),
26
27
28 62 10% (30-39), 20% (40-49), 30% (50-59), 50% (60-69), and 60% (70-74). Compared to
29
30
31 63 individuals aged 20-39 without multimorbidity, those with multimorbidity had a higher
32
33
34 64 incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-2.56] in ages 20-
35
36
37 65 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
38
39
40 66 ages ≥ 60). The difference in the incidence of clinical events between multimorbidity and
41
42
43 67 no-multimorbidity was larger than that between age groups.
44
45

46 68 **Conclusions**

47
48
49 69 Multimorbidity is already prevalent in the middle-aged generation and is associated with
50
51
52 70 poor clinical outcomes. These findings underscore the significance of multimorbidity and
53
54
55 71 highlight the urgent need for preventive intervention at the public health care level.
56
57
58
59
60

72

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 73 **Article Summary**
5
6

7 74
8
9

10 75 Strengths and limitations of this study
11
12

13 76 • The current study covers a wide age range of individuals from a nationwide
14
15
16 77 general population.
17

18
19 78 • Japan`s high medical insurance coverage rate made it possible to
20
21
22 79 comprehensively identify chronic diseases from receipts.
23
24

25 80 • Longitudinal analysis enabled the examination of clinical outcomes of multiple
26
27
28 81 co-morbidities.
29
30

31 82 • The prevalence of multimorbidity may be underestimated because the target
32
33
34 83 population comprised regular employees and their families and might
35
36
37 84 accordingly be healthier than the general population.
38
39

40 85
41
42

43 86 **Keywords**
44
45

46 87 chronic disease, insurance claims, middle age, multimorbidity, preventive medicine
47
48
49 88
50
51
52
53
54
55
56
57
58
59
60

89 Introduction

90 Aging societies worldwide face the problem of how to provide adequate and
91 affordable health care for a growing number of patients with multiple chronic conditions,
92 termed multimorbidity.^{1,2} Managing multimorbidity is becoming a global challenge on the
93 clinical and public healthcare level not only in high-, but also in low- and middle-income
94 countries.³ Many epidemiological studies on multimorbidity have shown its association
95 with age, socio-demographic and socio-economic factors.⁴⁻⁷ In addition, numerous
96 studies have shown that multiple comorbidities are common in older people.⁸⁻¹¹ It has
97 been reported that multimorbid older patients had more than twice as many contacts per
98 year with physicians than those without multimorbidity¹² and that the likelihood of being
99 hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.⁸ On the
100 other hand, the accumulation of chronic diseases occurs continuously from middle age.
101 A number of recent studies conducted in various countries have reported that the onset
102 of multimorbidity is shifting towards younger age groups.^{6, 13-15} However, multimorbidity
103 studies tend to focus on older people, and in-depth knowledge on multimorbidity in
104 younger age groups is lacking.

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

1
2
3
4 107 cohort. Our findings add to existing knowledge by showing that multimorbidity has a
5
6
7 108 significant impact on health starting from middle age and underscore the need for
8
9
10 109 preventive intervention on the public health care level.
11

12 110
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

111 **Materials and Methods**

112 *Data source*

113 We used the nationwide medical claims and enrolment data of the Health Insurance
114 Association for Architecture and Civil Engineering companies (HIA²CE), which is one of
115 the largest social insurance associations in Japan. HIA²CE is a comprehensive insurer
116 which includes 1700 companies, from small engineering companies to middle and large
117 construction companies across Japan. This claims database covers a total of 400 000
118 insured persons, consisting of employees and their dependents.

119 Japan has maintained a universal health coverage system since 1961. All medical
120 information regarding clinical practice covered by this health insurance is included in the
121 medical claims data, except for self-financed medical care and individuals who receive
122 public assistance. Furthermore, medical facilities have been obliged since 2011 to
123 submit medical claims data as an electronic record. Medical claims data include the
124 names of the diagnosed diseases, the names of medical procedures, and the names of
125 prescribed medications, among others. In the present study, we extracted the age, sex,
126 names and ICD-10 codes of diagnosed diseases, and hospitalisations and deaths from
127 the medical claims data in HIA²CE from FY2014 to FY2018 (April 2014 to March 2019).

1
2
3
4 128 The enrolment data from HIA²CE includes the medical characteristics of insured
5
6
7 129 persons as of April 2019.
8
9

10 130

11
12
13 131 *Research design and study population*
14
15

16 132 We prepared two data sets for analysis. The first data set contained baseline data of
17
18
19 133 FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The
20
21
22 134 study population for this baseline data set included individuals aged 20 to 74 years
23
24
25 135 insured in FY2014 (April 2014 to March 2015). Participants younger than 20 and older
26
27
28 136 than 75 years in FY2014 as well as participants who died during FY2014 were excluded
29
30
31 137 (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to
32
33
34 138 FY2018 (April 2014 to March 2019). We used this cohort data set to conduct Cox
35
36
37 139 regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).
38
39

40 140

41
42
43 141 *Definition of diagnosed diseases and multimorbidity*
44
45

46 142 The Charlson Comorbidity Index (CCI) is a validated tool which has been widely used
47
48
49 143 to assess patient comorbidities.¹⁶ The CCI Canadian version has been reported to be
50
51
52 144 applicable to Japanese claims data.¹⁷ We therefore defined diagnosed diseases using
53
54
55 145 medical claims data following ICD-10 codes of the CCI Canada version. We merged the
56
57
58
59

1
2
3
4 146 conditions “diabetes with chronic complication” and “diabetes without chronic
5
6
7 147 complication” into “diabetes mellitus”, and “mild liver disease” and “moderate or severe
8
9
10 148 liver disease” into “liver disease”. The following 15 chronic conditions were included:
11
12
13 149 AIDS/HIV, any malignancy (including lymphoma and leukaemia), cerebrovascular
14
15
16 150 disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes
17
18
19 151 mellitus, hemiplegia or paraplegia, metastatic solid tumour, liver disease, myocardial
20
21
22 152 infarction, peptic ulcer disease, renal disease, and rheumatologic disease. The ICD-10
23
24
25 153 codes of these diseases are shown in eTable 1 in the Supplement. Multimorbidity status
26
27
28 154 was defined as the concurrent presence of two or more (≥ 2) diagnosed diseases among
29
30
31 155 these conditions.^{18,19}
32
33

156

157 *Definition of outcome events; hospitalisation and death*

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

1
2
3
4 1645
6
7 165 *Estimation of diagnosed disease prevalence to nationwide scale*
8
9

10 166 Diagnosed disease prevalence from baseline data was standardised to the
11
12
13 167 nationwide Japanese total population. We calculated diagnosed disease prevalence
14
15
16 168 according to 5-year age brackets and gender and applied it to the same age and gender
17
18
19 169 groups of the vital statistics 2014 in Japan.²²
20
21

22 170

23
24
25 171 *Effect of multimorbidity by age group*
26
27

28 172 To examine the effect of multimorbidity by age group, we performed Cox regression
29
30
31 173 analysis using cohort data from four consecutive years (FY2015 to FY2018). To
32
33
34 174 examine the independent and additive effect of multimorbidity and aging, we defined
35
36
37 175 combined categories according to three age groups representing “young”, “middle”, and
38
39
40 176 “old” ages (20-39, 40-59, and ≥ 60 , respectively) and the binary status of multimorbidity,
41
42
43 177 with the reference set as no multimorbidity individuals aged 20-39.
44
45

46 178

47
48
49 179 *Statistical analysis*
50
51

52 180 Effects of multimorbidity by age groups were analysed using Cox regression as
53
54
55 181 described under the heading “Effect of multimorbidity by age group”. Results were
56
57
58
59
60

1
2
3
4 182 considered statistically significant at a two-sided P -value of less than 0.05. All analyses
5
6
7 183 were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX,
8
9
10 184 USA).

11
12
13 185

14
15
16 186 *Patient and Public involvement*

17
18
19 187 Patients or the public were not involved in this research. However, the results of this
20
21
22 188 study will be disseminated to the public through various means including published
23
24
25 189 papers and presentations.

26
27 190
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

191 **Results**

192 *Study participants*

193 We analysed $n = 246\ 671$ individuals in the baseline data set in FY2014 and $n = 181$
194 959 individuals in the cohort data set FY2014-FY2018. Because follow-up was four
195 years, the cohort data set was slightly smaller than the baseline data set, especially as
196 a number of young individuals aged 20-24 and older individuals aged >60 dropped out.
197 This may be due to raising children or early retirement, and explains the higher
198 proportion of men in the cohort data set. Mean age and co-morbidity numbers among
199 CCI diseases were mostly comparable between the two data sets, although the
200 prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic
201 pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in
202 disease prevalence between genders were observed. Notably, men had a higher
203 prevalence of diabetes mellitus ($P = 0.001$) whereas women had a higher prevalence of
204 chronic pulmonary disease ($P = 0.002$).

205

206 *Estimated prevalence of multimorbidity in the Japanese total population*

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

1
2
3
4 209 estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population
5
6
7 210 (Table 1). The prevalence of multimorbidity increased with age, i.e., 25-24 (3.9%), 25-29
8
9
10 211 (7.7%), 30-34 (9.7%), 35-39 (12.5%), 40-44 (14.6%), 45-49 (19.0%), 50-54 (25.9%), 55-
11
12
13 212 59 (33.2%), 60-64 (40.7%), 65-69 (49.9%), and 70-74 (60.1%) (Fig. 2A). Figure 2B
14
15
16 213 shows the types of disease and their prevalence across age groups. The top five
17
18
19 214 diseases across the age groups “young” (20-39), “middle-age (40-59), and “old” (60-74)
20
21
22 215 in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer disease,
23
24
25 216 liver disease, diabetes mellitus, and any malignancy; “middle-age”: chronic pulmonary
26
27
28 217 disease, diabetes mellitus, liver disease, peptic ulcer disease, and any malignancy; and
29
30
31 218 “old”: diabetes mellitus, chronic pulmonary disease, liver disease, peptic ulcer disease,
32
33
34 219 and cerebrovascular disease. Notably, diabetes mellitus moved up across the age
35
36
37 220 groups from ranking fourth to first. Details of the prevalence of specific diseases are
38
39
40 221 shown in eTable 3 in the Supplement. In Figure 2C, disease prevalence is shown in
41
42
43 222 comparison to disease prevalence in the 40-44 age group. After the age of 40-44, the
44
45
46 223 top five accelerating diseases were dementia, cerebrovascular disease, peripheral
47
48
49 224 vascular disease, metastatic tumour, and congestive heart failure.
50
51

52 225
53
54
55
56
57
58
59
60

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	10.3	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	10.1	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	12.8	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

1
2
3 Values are numbers (%) unless otherwise stated.

4 ^aAny malignancy includes leukemia and lymphoma.

5 FY; fiscal year

6 SD; standard deviation

7 CCI; Charlson Comorbidity Index

8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

1
2
3
4 229 *Effect of multimorbidity by age group*

5
6
7 230 Cox regression analysis showed that young individuals aged 20-39 with
8
9
10 231 multimorbidity had a higher hazard ratio (HR) compared to the same age group without
11
12
13 232 multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age
14
15
16 233 groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages
17
18
19 234 ≥ 60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR =
20
21
22 235 1.62 [95% CI, 1.56-1.69] ages ≥ 60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59
23
24
25 236 without multimorbidity) (Fig. 3). We also assessed HRs for non-multimorbid and
26
27
28 237 multimorbid women and men separately and found that women had a lower HR than
29
30
31 238 men in the 20-39 age group but a higher HR than men in the ≥ 60 age group (eTable 4
32
33
34 239 in the Supplement).

241 Discussion

242 In this study we analysed nationwide medical claims data for 15 chronic diseases in a
243 large cohort of the general population of Japan. As key findings, standardised
244 prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for
245 women. Further, age group-specific prevalence rates for multimorbidity ranged from
246 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an
247 accelerating increase after age 40. Importantly, significant differences in the clinical
248 outcomes of multimorbidity versus no multimorbidity were already present in young and
249 middle-aged individuals.

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

1
2
3
4 259 individuals already suffering from other chronic diseases,^{23,24} younger people,²⁵ and
5
6
7 260 people with a low socio-economic status.²⁶ Such diseases often remain undiagnosed or
8
9
10 261 underreported in health records.²⁷ These limitations likely contributed to an
11
12
13 262 underestimation of multimorbidity in our cohort. Further, because we did not manually
14
15
16 263 verify the presence of disease using the physician's medical records data or medication
17
18
19 264 information, disease names extracted from the medical claims data might be incorrect in
20
21
22 265 some cases. In particular, Japanese physicians sometimes change the name of the
23
24
25 266 disease in the medical record to the "correct" disease name for the medication they wish
26
27
28 267 to prescribe, a practice called "disease name for claims data".

31 268 Because of differences in data sources and study populations, direct comparison of
32
33
34 269 population-based prevalence rates between studies is not straightforward. Nonetheless,
35
36
37 270 the standardised prevalence rates for multimorbidity as reported in the present study -
38
39
40 271 26.1% for men and 26.0% for women - are similar to those reported by recent studies in
41
42
43 272 other high-income countries, such as the United States (25% in men, 25% in women),²⁸
44
45
46 273 England (24.4% in men, 30% in women),²⁶ Canada (24.3% whole population),⁵ and
47
48
49 274 Denmark (19.3% in men, 23.7% in women).⁶ Many previous studies on multimorbidity
50
51
52 275 focused on the older generation, aged 65 and up, because of the larger number of
53
54
55 276 chronic diseases in this age group and the increasing number of people entering it.

1
2
3
4 277 However, our present data show that already approximately 10% of 30-34-, 19% of 45-
5
6
7 278 49-, and 33% of 55-59-year-olds have ≥ 2 chronic diseases. Further, 1% of 30-34-, 4%
8
9
10 279 of 45-49-, and 9% of 55-59-year-olds have ≥ 5 chronic diseases. These results show
11
12
13 280 that multimorbidity is already prominent in the middle-aged population. Recent studies
14
15
16 281 reported similar or slightly higher prevalence rates for ≥ 2 chronic diseases in an
17
18
19 282 American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)²⁵ and a Canadian (10.5% of
20
21
22 283 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)⁵ population, although these two
23
24
25 284 studies also included mental diseases and osteoporosis, which our present study did
26
27
28 285 not. Our present study shows that, among 15 chronic diseases, the top five diseases in
29
30
31 286 the 55-64 age group are chronic pulmonary disease (20.4-23.1%), diabetes mellitus
32
33
34 287 (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer disease (15.6-18.2%), and any
35
36
37 288 malignancy (8.2-10.7%). With regard to diabetes mellitus, prevalence in the present
38
39
40 289 study is similar to that previously reported in an American population (15-30% in
41
42
43 290 individuals aged 55-65)²⁵ but higher than that in a Canadian population (16.6% in
44
45
46 291 individuals aged 55-64)⁴. The prevalence of chronic pulmonary disease in our present
47
48
49 292 55-65-year-olds was almost twice as high as those seen for the combined prevalence of
50
51
52 293 asthma and chronic obstructive pulmonary disease (COPD) in an American population
53
54
55 294 aged 55-65 years (5% for men and 10% for women)²⁵ and in a Canadian population

1
2
3
4 295 aged 55-64 years (13.7%).⁵ This difference might have arisen due to our inclusion of
5
6
7 296 various other pulmonary diseases besides asthma and COPD. Regarding liver disease,
8
9
10 297 the prevalence seen for 55-65-year-olds in the present study was comparable to that
11
12
13 298 seen in an adult population in Northern Italy²⁹ and in an adult population in Korea,³⁰
14
15
16 299 although this comparison requires care since the types of liver disease in these studies
17
18
19 300 and the age groups included vary.

22 301 Analysis of clinical outcomes using Cox regression revealed that the presence of
23
24
25 302 multimorbidity increased HRs in all age groups, including young individuals. In addition,
26
27
28 303 comparison of the increased HRs resulting from multimorbidity versus no multimorbidity
29
30
31 304 showed that the impact of multimorbidity exceeds that of increasing age. These results
32
33
34 305 indicate that multimorbidity places a burden on all age groups.

37 306 Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary
38
39
40 307 disease, liver disease, peptic ulcer disease, and any malignancy) in the present study
41
42
43 308 are lifestyle-related diseases that develop slowly over time. This trend should be
44
45
46 309 greeted with alarm. We trust that this study raises awareness of the potential health
47
48
49 310 risks and burden associated with the early onset of multimorbidity in young and middle-
50
51
52 311 age, the period when one is busy working and raising children. Future studies should
53
54
55 312 investigate the specific lifestyle factors associated with an elevated risk of multimorbidity
56
57
58
59
60

1
2
3
4 313 in the Japanese working population. Ultimately, public health care policies should be
5
6
7 314 aimed at efforts to reverse the trend toward early multimorbidity onset.
8
9

10 315 In conclusion, the present study revealed that the impact of multimorbidity is already
11
12
13 316 prominent in middle-aged Japanese, with elevated adverse events such as
14
15
16 317 hospitalisation and death. In addition, the risk posed by multimorbidity exceeds that of
17
18
19 318 aging in all age groups. These results underscore the need to undertake healthcare
20
21
22 319 intervention against the onset of multimorbidity before middle-age, and not to leave it as
23
24
25 320 a problem for geriatricians.
26
27

28 321

31 322 **Ethical Approval**

32
33
34 323 The present study was approved by the Institutional Review Board (IRB) of Kyoto
35
36
37 324 University (approval number: R0817). All data were anonymised before analysis and
38
39
40 325 none of the researchers had access to patient-identifiable information. The IRB waived
41
42
43 326 informed consent for this observational study.
44
45

46 327

49 328 **Data Availability Statement**

50
51
52 329 All data are incorporated into the article and its online supplementary material.
53
54

55 330
56
57
58
59
60

1
2
3
4 331 **Author Contributions**
5

6
7 332 Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors.
8
9

10 333 Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important
11
12

13 334 intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS.
14
15

16 335 Administrative, technical, or material support: YS, SF. Study supervision: SF, TN.
17
18

19 336 YS had full access to all the data in the study and takes responsibility for the integrity of
20
21

22 337 the data and the accuracy of the data analysis. All authors gave final approval and
23
24

25 338 agreed to be accountable for all aspects of work.
26
27

28 339
29
30

31 340 **Acknowledgements**
32
33

34 341 The authors are grateful to HIA²CE for providing data for the present study.
35
36

37 342
38
39

40 343 **Funding**
41
42

43 344 This work was supported by Grants-in-Aid from the Japan Society for the Promotion of
44
45

46 345 Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in
47
48

49 346 the design of the study; in the collection, analysis and interpretation of data; in the
50
51

52 347 writing of the report; or in the decision to submit the article for publication.
53
54

55 348
56
57
58
59
60

1
2
3
4 349 **Competing Interests**

5
6
7 350 None declared.

8
9
10 351

11
12
13 352 **Patient Consent for Publication**

14
15
16 353 Not applicable.

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

355 **References**

356

- 357 1 Bleich SN, Sherrod C, Chiang A, *et al.* Systematic Review of Programs Treating
358 High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities
359 in the United States, 2008-2014. *Prev Chronic Dis.* Nov 12 2015;12:E197.
360 doi:10.5888/pcd12.150275
- 361 2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative
362 review. *Prev Med Rep.* Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008
- 363 3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y,
364 Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of
365 multimorbidity in a middle-income country. *PLoS One.* 2020;15(12):e0243614.
366 doi:10.1371/journal.pone.0243614
- 367 4 Low LL, Kwan YH, Ko MSM, *et al.* Epidemiologic Characteristics of Multimorbidity
368 and Sociodemographic Factors Associated With Multimorbidity in a Rapidly
369 Aging Asian Country. *JAMA Netw Open.* Nov 1 2019;2(11):e1915245.
370 doi:10.1001/jamanetworkopen.2019.15245
- 371 5 Pefoyo AJ, Bronskill SE, Gruneir A, *et al.* The increasing burden and complexity of
372 multimorbidity. *BMC Public Health.* Apr 23 2015;15:415. doi:10.1186/s12889-
373 015-1733-2

- 1
2
3 374 6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the
4
5 prevalence of multimorbidity - A register-based population study. *BMC Public*
6 375
7 *Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8
8 376
9
10 377 7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of
11
12 multimorbidity on healthcare utilisation and work productivity by socioeconomic
13 378
14 groups: Cross-sectional analyses of Australia and Japan. *PLoS One*.
15 379
16 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281
17 380
18
19 381 8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization
20
21 and costs in an elderly community-dwelling population: a claims data based
22 382
23 observational study. *BMC Health Serv Res*. Jan 22 2015;15:23.
24 383
25 doi:10.1186/s12913-015-0698-2
26 384
27
28 385 9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-
29
30 specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-
31 386
32 sectional study based on nationwide claims data. *BMJ Open*. Jun 9
33 387
34 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333
35 388
36
37 389 10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in
38
39 relation to age, gender and immigrant status: a cross-sectional study based on
40 390
41 administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812.
42 391
43 doi:10.1136/bmjopen-2016-012812
44 392
45
46 393 11 Picco L, Achilla E, Abdin E, *et al*. Economic burden of multimorbidity among older
47
48 adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10
49 394
50 2016;16:173. doi:10.1186/s12913-016-1421-7
51 395
52
53
54
55
56
57
58
59
60

- 1
2
3 396 12 van den Bussche H, Schon G, Kolonko T, *et al.* Patterns of ambulatory medical
4
5 397 care utilization in elderly patients with special reference to chronic diseases and
6
7 398 multimorbidity--results from a claims data based observational study in Germany.
9
10 399 *BMC Geriatr.* Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54
11
12 400 13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of
13
14 401 risk factors to socioeconomic inequalities in multimorbidity across the lifecourse:
15
16 402 a longitudinal analysis of the Twenty-07 cohort. *BMC Med.* Aug 24
17
18 403 2017;15(1):152. doi:10.1186/s12916-017-0913-6
19
20
21 404 14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising
22
23 405 burden of multimorbidity and related socio-demographic factors: a repeated
24
25 406 cross-sectional study of Ontarians. *Can J Public Health.* Apr 13
26
27 407 2021;doi:10.17269/s41997-021-00474-y
28
29
30
31 408 15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in
32
33 409 multimorbidity, complex multimorbidity and multiple functional limitations in the
34
35 410 ageing population of England, 2002-2015. *J Comorb.* Jan-Dec
36
37 411 2019;9:2235042X19872030. doi:10.1177/2235042X19872030
38
39
40 412 16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying
41
42 413 prognostic comorbidity in longitudinal studies: development and validation. *J*
43
44 414 *Chronic Dis.* 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-8
45
46
47 415 17 Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson comorbidity
48
49 416 index and score for risk adjustment in hospital discharge abstracts using data
50
51 417 from 6 countries. *Am J Epidemiol.* Mar 15 2011;173(6):676-82.
52
53 418 doi:10.1093/aje/kwq433
54
55
56
57
58
59
60

- 1
2
3 419 18 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring
4
5 420 multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*.
6
7 421 Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098
8
9
10 422 19 Le Reste JY, Nabbe P, Manceau B, *et al*. The European General Practice
11
12 423 Research Network presents a comprehensive definition of multimorbidity in
13
14 424 family medicine and long term care, following a systematic review of relevant
15
16 425 literature. *J Am Med Dir Assoc*. May 2013;14(5):319-25.
17
18 426 doi:10.1016/j.jamda.2013.01.001
19
20
21 427 20 Ooba N, Setoguchi S, Ando T, *et al*. Claims-based definition of death in Japanese
22
23 428 claims database: validity and implications. *PLoS One*. 2013;8(5):e66116.
24
25 429 doi:10.1371/journal.pone.0066116
26
27
28 430 21 Sakai M, Ohtera S, Iwao T, *et al*. Validation of claims data to identify death among
29
30 431 aged persons utilizing enrollment data from health insurance unions. *Environ*
31
32 432 *Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3
33
34
35 433 22 Statistics Bureau of Japan. Preliminary count of the Japanese population.
36
37 434 Accessed March, 2014. <http://www.stat.go.jp/data/jinsui/index.html>
38
39
40 435 23 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns
41
42 436 and depressive symptoms: a nationwide cross-sectional study in Japan. *Fam*
43
44 437 *Med Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234
45
46
47 438 24 Egede LE. Major depression in individuals with chronic medical disorders:
48
49 439 prevalence, correlates and association with health resource utilization, lost
50
51 440 productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct
52
53 441 2007;29(5):409-16. doi:10.1016/j.genhosppsy.2007.06.002
54
55
56
57
58
59
60

- 1
2
3 442 25 Rocca WA, Boyd CM, Grossardt BR, *et al.* Prevalence of multimorbidity in a
4
5 443 geographically defined American population: patterns by age, sex, and
6
7 444 race/ethnicity. *Mayo Clin Proc.* Oct 2014;89(10):1336-49.
8
9 445 doi:10.1016/j.mayocp.2014.07.010
10
11
12 446 26 Cassell A, Edwards D, Harshfield A, *et al.* The epidemiology of multimorbidity in
13
14 447 primary care: a retrospective cohort study. *Br J Gen Pract.* Apr
15
16 448 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465
17
18
19 449 27 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al.* Comparison of the
20
21 450 information provided by electronic health records data and a population health
22
23 451 survey to estimate prevalence of selected health conditions and multimorbidity.
24
25 452 *BMC Public Health.* Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251
26
27
28 453 28 St Sauver JL, Boyd CM, Grossardt BR, *et al.* Risk of developing multimorbidity
29
30 454 across all ages in an historical cohort study: differences by sex and ethnicity.
31
32 455 *BMJ Open.* Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413
33
34
35 456 29 Bellentani S, Tiribelli C, Saccoccio G, *et al.* Prevalence of chronic liver disease in
36
37 457 the general population of northern Italy: the Dionysos Study. *Hepatology.* Dec
38
39 458 1994;20(6):1442-9. doi:10.1002/hep.1840200611
40
41
42 459 30 Park SH, Plank LD, Suk KT, *et al.* Trends in the prevalence of chronic liver
43
44 460 disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol.* Apr
45
46 461 2020;26(2):209-215. doi:10.3350/cmh.2019.0065
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 463 **Figure Legends**
4

5 464 **Figure 1.** Participant selection flowchart. FY; fiscal year
6
7

8 465
9
10 466 **Figure 2.** Multimorbidity across age groups in the Japanese total population aged 20-
11
12 74. **A)** Percentage of the population having 0 to ≥ 5 chronic diseases by age group. **B)**
13
14 467
15 468 Prevalence of the top ten chronic diseases by age group. **C)** The top ten chronic
16
17 469 diseases with the steepest increase after age 40-44 years.
18
19

20 470
21
22 471 **Figure 3.** Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2
23
24 472 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese
25
26 473 aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval
27
28

29 474

30
31 475

32
33 476 **Supplementary Information**
34

35 477 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define
36
37
38 478 diseases in medical claims data
39

40 479 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and
41
42 480 cohort data
43

44
45 481 **Supplementary eTable 3.** Diagnosed disease prevalence in fiscal year 2014 applied to
46
47 482 the Japanese total population by age group
48

49 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on
50
51 hospitalisation and death rates in a 5-year cohort of $n = 111\ 088$ men and
52
53
54 $n = 70\ 871$ women. Cox regression analysis
55
56
57
58
59

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

483

For peer review only

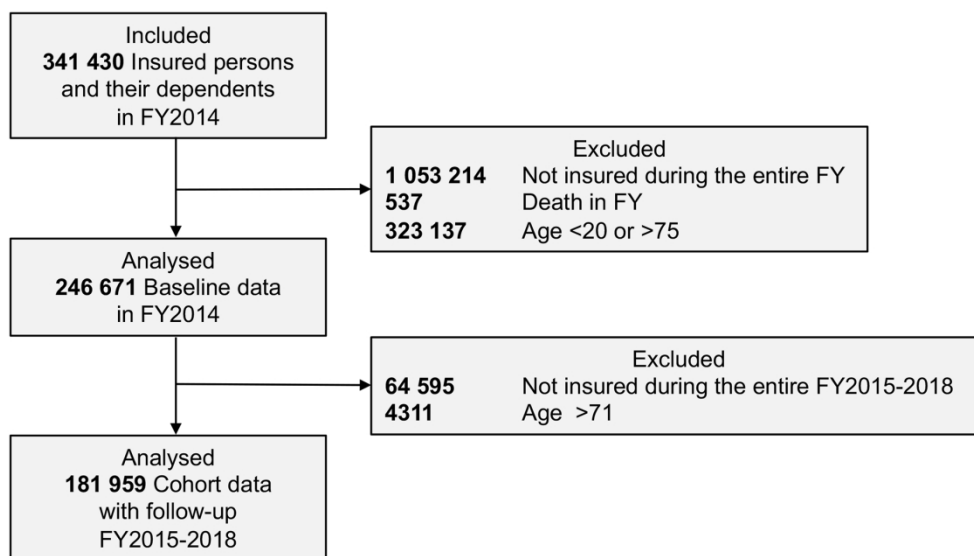


Figure 1. Participant selection flowchart. FY; fiscal year

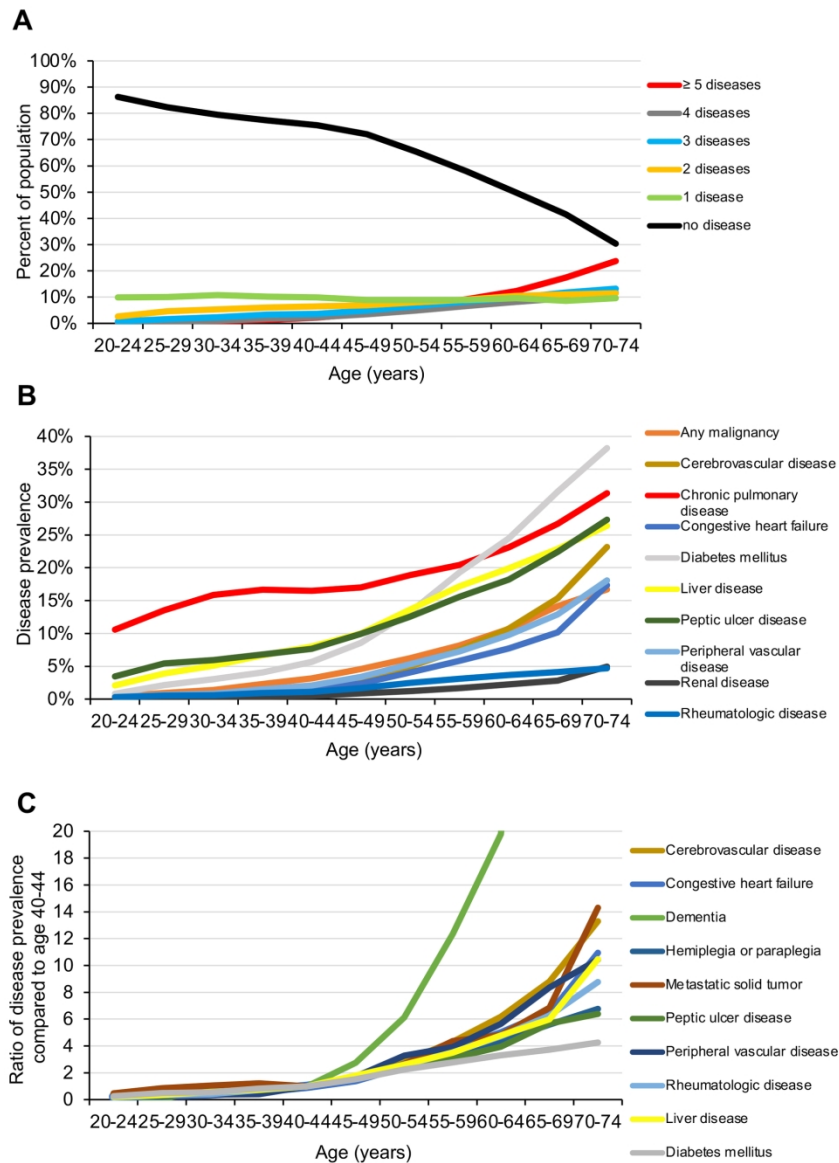


Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. **A)** Percentage of the population having 0 to ≥ 5 chronic diseases by age group. **B)** Prevalence of the top ten chronic diseases by age group. **C)** The top ten chronic diseases with the steepest increase after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

161x230mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

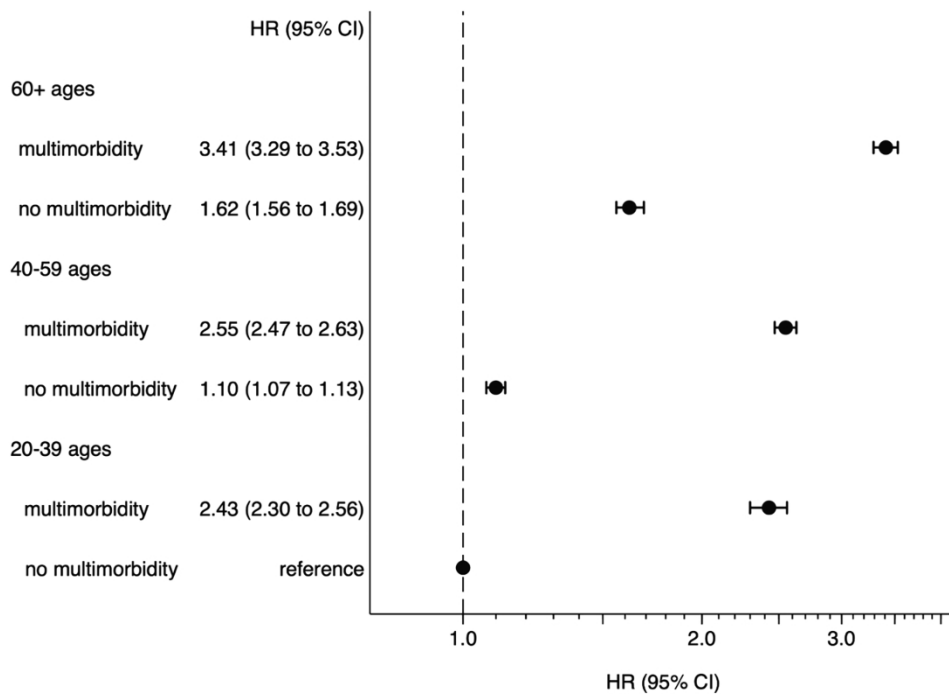


Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

139x103mm (600 x 600 DPI)

1
2
3 Supplementary material
4
5

6 Title: The burden of multimorbidity across generations in Japan 2014-2019 - a historical cohort study using nationwide
7 medical claims data
8
9

10
11 Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD
12
13

14
15
16 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define diseases in medical claims data
17

18 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and cohort data
19

20 **Supplementary eTable 3.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population by
21 age group
22

23
24 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on hospitalisation and death rates in a 5-year
25 cohort of $n = 111\,088$ men and $n = 70\,871$ women. Cox regression analysis
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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
<i>N</i>	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
<i>N</i>					
	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%)

^aAny 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%)

^aAny 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%)

^aAny 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%)

^aAny 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

^aReferences are female for sex, no disease for morbidity variables

^bReference 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 (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Suppl. Table 2 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 (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	16, Fig. 3
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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **1 Title**

5
6
7 2 The prevalence of multimorbidity and its associations with hospitalisation or death in
8
9
10 3 Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in
11
12
13 4 the middle-aged generation

14
15
16 **5 Authors**

17
18
19 6 Yoshiyuki Saito^{1,2*} PharmD, Ataru Igarashi^{1,3} PhD, Takeo Nakayama² MD PhD, Shingo
20
21
22 7 Fukuma⁴ MD

23
24
25
26
27
28 **9 Author Affiliations**

29
30
31 10 ¹Department of Health Economics & Outcomes Research, Graduate School of
32
33
34 11 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo
35
36
37 12 113-0033, Japan

38
39
40 13 ²Department of Health Informatics, School of Public Health, Graduate School of
41
42
43 14 Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

44
45
46 15 ³Unit of Public Health and Preventive Medicine, Yokohama City University School of
47
48
49 16 Medicine, Kanagawa 236-0027, Japan

50
51
52 17 ⁴School of Human Health Sciences, Graduate School of Medicine, Kyoto University,
53
54
55 18 Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

1
2
3
4 195
6
7 20 **Running head**8
9
10 21 The burden of multimorbidity in Japan 2014-201911
12
13 2214
15
16 23 ***Corresponding author**17
18
19 24 Yoshiyuki Saito, PharmD20
21
22 25 Department of Health Economics & Outcomes Research, Graduate School of23
24
25 26 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo26
27
28 27 113-0033, Japan29
30
31 28 E-mail: saito.yoshiyuki.86x@kyoto-u.jp32
33
34 29 Tel: +81-3-5841-482835
36
37 3038
39
40 31 Word count: 3492 (incl. abstract)41
42
43 32 Tables: 144
45
46 33 Figures: 347
48
49 34 Supplementary Tables: 450
51
52 3553
54
55 36

1
2
3
4 37 **Abstract**

5
6
7 38 **Objective**

8
9
10 39 To describe the prevalence of multimorbidity and its associations with clinical outcomes
11
12
13 40 across age groups.

14
15
16 41 **Design**

17
18
19 42 Retrospective cohort study using nationwide medical claims data.

20
21
22 43 **Setting**

23
24
25 44 Carried out in Japan between April 2014 and March 2019.

26
27
28 45 **Participants**

29
30
31 46 N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance
32
33
34 47 Association for Architecture and Civil Engineering companies (HIA²CE) were included
35
36
37 48 into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals
38
39
40 49 were included into the cohort data set spanning FY2014-FY2018.

41
42
43 50 **Exposures**

44
45
46 51 Multimorbidity was defined as having ≥ 2 of 15 chronic conditions according to the ICD-
47
48
49 52 10 codes of the Charlson Comorbidity Index.

50
51
52 53 **Primary and Secondary Outcomes**

1
2
3
4 54 Primary outcome: The standardised prevalence of multimorbidity across age groups
5
6
7 55 was evaluated using data from FY 2014 and extrapolated to the Japanese total
8
9
10 56 population. Secondary Outcome: Hospitalisation or death events were traced by month
11
12
13 57 using medical claims data and insurer enrolment data. Associations between
14
15
16 58 multimorbidity and 5-year hospitalisation and/or death events across age groups were
17
18
19 59 analysed using a Cox regression model.
20
21

22 60 **Results**

23
24
25 61 The standardised prevalence rate of multimorbidity in nationwide Japanese total
26
27
28 62 population was approximately 5% (ages 25-24 (3.9%), 25-29 (7.7%)), 10% (30-34
29
30
31 63 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-
32
33
34 64 59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).
35
36

37 65 Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity
38
39
40 66 had a higher incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-
41
42
43 67 2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41 [95%
44
45
46 68 CI, 3.23-3.53] in ages ≥ 60). The difference in the incidence of clinical events between
47
48
49 69 multimorbidity and no-multimorbidity was larger than that between age groups.
50
51

52 70 **Conclusions**

1
2
3
4 71 Multimorbidity is already prevalent in the middle-aged generation and is associated with
5
6
7 72 poor clinical outcomes. These findings underscore the significance of multimorbidity and
8
9
10 73 highlight the urgent need for preventive intervention at the public health care level.
11
12

13 74
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4 75 **Article Summary**
5
6

7 76
8
9

10 77 Strengths and limitations of this study
11
12

13 78 • The current study covers a wide age range of individuals from a nationwide

14
15
16 79 general population.
17

18
19 80 • Japan`s high medical insurance coverage rate made it possible to

20
21
22 81 comprehensively identify chronic diseases from receipts.
23
24

25 82 • Longitudinal analysis enabled the examination of clinical outcomes of multiple

26
27
28 83 co-morbidities.
29
30

31 84 • The prevalence of multimorbidity may be underestimated because the target

32
33
34 85 population comprised regular employees and their families and might

35
36
37 86 accordingly be healthier than the general population.
38
39

40 87
41
42

43 88 **Keywords**
44
45

46 89 chronic disease, insurance claims, middle age, multimorbidity, preventive medicine
47
48

49 90
50
51
52
53
54
55
56
57
58
59
60

91 Introduction

92 Aging societies worldwide face the problem of how to provide adequate and
93 affordable health care for a growing number of patients with multiple chronic conditions,
94 termed multimorbidity.^{1,2} Managing multimorbidity is becoming a global challenge on the
95 clinical and public healthcare level not only in high-, but also in low- and middle-income
96 countries.³ Many epidemiological studies on multimorbidity have shown its association
97 with age, socio-demographic and socio-economic factors.⁴⁻⁷ In addition, numerous
98 studies have shown that multiple comorbidities are common in older people.⁸⁻¹¹ It has
99 been reported that multimorbid older patients had more than twice as many contacts per
100 year with physicians than those without multimorbidity¹² and that the likelihood of being
101 hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.⁸ On the
102 other hand, the accumulation of chronic diseases occurs continuously from middle age.
103 A number of recent studies conducted in various countries have reported that the onset
104 of multimorbidity is shifting towards younger age groups.^{6, 13-15} However, multimorbidity
105 studies tend to focus on older people, and in-depth knowledge on multimorbidity in
106 younger age groups is lacking.

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

1
2
3
4 109 cohort. Our findings add to existing knowledge by showing that multimorbidity has a
5
6
7 110 significant impact on health starting from middle age and underscore the need for
8
9
10 111 preventive intervention on the public health care level.
11

12 112
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

113 **Materials and Methods**

114 *Data source*

115 We used the nationwide medical claims and enrolment data of the Health Insurance
116 Association for Architecture and Civil Engineering companies (HIA²CE), which is one of
117 the largest social insurance associations in Japan. HIA²CE is a comprehensive insurer
118 which includes 1700 companies, from small engineering companies to middle and large
119 construction companies across Japan. This claims database covers a total of 400 000
120 insured persons, consisting of employees and their dependents.

121 Insured-based data base is used widely and one of the popular real-world data in
122 Japan.¹⁶ Japan has maintained a universal health coverage system since 1961. All
123 medical information regarding clinical practice covered by this health insurance is
124 included in the medical claims data, except for self-financed medical care and
125 individuals who receive public assistance. Furthermore, medical facilities have been
126 obliged since 2011 to submit medical claims data as an electronic record. Medical
127 claims data include the names of the diagnosed diseases, the names of medical
128 procedures, and the names of prescribed medications, among others. In the present
129 study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and
130 hospitalisations and deaths from the medical claims data in HIA²CE from FY2014 to

1
2
3
4 131 FY2018 (April 2014 to March 2019). The enrolment data from HIA²CE includes the
5
6
7 132 medical characteristics and in-out information of insured persons as of April 2019.
8
9

10 133

11
12
13 134 *Research design and study population*
14
15

16 135 We prepared two data sets for analysis. The first was cross-sectional data set
17
18
19 136 contained baseline data of FY2014, which we used to describe the diagnosed disease
20
21
22 137 prevalence in FY2014. The study population for this baseline data set included
23
24
25 138 individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since
26
27
28 139 HIA²CE is a type of insurance for workers in Japan, database include only under 75
29
30
31 140 years individuals. Therefore, maximum age in this cohort was 74 years. Participants
32
33
34 141 younger than 20 in FY2014 as well as participants who died during FY2014 were
35
36
37 142 excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period,
38
39
40 143 FY2014 to FY2018 (April 2014 to March 2019). Second data set contained participants
41
42
43 144 insured in whole period. We used this cohort data set to conduct Cox regression
44
45
46 145 analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).
47
48

49 146

50
51
52 147 *Definition of diagnosed diseases and multimorbidity*
53
54
55
56
57
58
59
60

1
2
3
4 148 There are a variety of definitions for chronic conditions in multimorbidity studies.¹⁷⁻¹⁹
5
6
7 149 We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the
8
9
10 150 diseases associated with a significant risk of clinical events.²⁰ The reason, we used CCI,
11
12
13 151 was that we focused on describing the prevalence of each disease and also assessing
14
15
16 152 the association of multimorbidity on hospitalisation or death. The CCI Canadian version
17
18
19 153 has been reported to be applicable to Japanese claims data.²¹ We therefore defined
20
21
22 154 diagnosed diseases using medical claims data following ICD-10 codes of the CCI
23
24
25 155 Canada version. We merged the conditions “diabetes with chronic complication” and
26
27
28 156 “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease”
29
30
31 157 and “moderate or severe liver disease” into “liver disease”. The following 15 chronic
32
33
34 158 conditions were included: AIDS/HIV, any malignancy (including lymphoma and
35
36
37 159 leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart
38
39
40 160 failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour,
41
42
43 161 liver disease, myocardial infarction, peptic ulcer disease, renal disease, and
44
45
46 162 rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in
47
48
49 163 the Supplement. Multimorbidity status was defined as the concurrent presence of two or
50
51
52 164 more (≥ 2) diagnosed diseases among these conditions.^{22, 23} We only used confirmed
53
54
55 165 diagnoses, not including suspected diagnoses, in Japanese claims data.
56
57
58
59
60

1
2
3
4 1665
6
7 167 *Definition of outcome events; hospitalisation or death*
8
9

10 168 We defined two composite outcomes, hospitalisation or death, which occurred during
11
12
13 169 the period from FY2015 to FY2018. Using the medical claims data, both events were
14
15
16 170 traced by month. In Japan, the validity of death event information is reported to be less
17
18
19 171 sensitive if derived from medical claims data only.^{24, 25} Therefore, we also used death
20
21
22 172 information from enrolment data recorded by the insurer: if either contained death
23
24
25 173 information, this was defined as a death event.
26
27

28 174

30
31 175 *Estimation of diagnosed disease prevalence to nationwide scale*
32
33

34 176 Diagnosed disease prevalence from baseline data was standardised to the
35
36
37 177 nationwide Japanese total population. We calculated prevalence rates according to
38
39
40 178 groups by 5-year age brackets and sex. Then, we estimated the prevalence rates
41
42
43 179 standardized to Japanese total population (age-sex standardized prevalence rate),
44
45
46 180 using the number from the vital statistics 2014 in Japan.²⁶
47
48

49 181

50
51
52 182 *The association of multimorbidity with outcome by age group*
53
54
55
56
57
58
59
60

1
2
3
4 183 To examine the association of multimorbidity with outcome by age group, we
5
6
7 184 performed Cox regression analysis adjusted by sex using cohort data from four
8
9
10 185 consecutive years (FY2015 to FY2018). The independent and additive effect of
11
12
13 186 multimorbidity and aging, we defined combined categories according to three age
14
15
16 187 groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥ 60 ,
17
18
19 188 respectively) and the binary status of multimorbidity, with the reference set as no
20
21
22 189 multimorbidity individuals aged 20-39. This model was able to show HR for aging alone
23
24
25 190 (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity
26
27
28 191 and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-
29
30
31 192 39 ages without multimorbidity).

32
33
34 193

35 36 37 194 *Statistical analysis*

38
39
40 195 Cox regression was conducted for the association of multimorbidity with outcome by
41
42
43 196 age group. Results were considered statistically significant at a two-sided *P*-value of
44
45
46 197 less than 0.05. All analyses were conducted using Stata software version 15.1
47
48
49 198 (StataCorp LLC; College Station, TX, USA).

50
51
52 199

53 54 55 200 *Patient and Public involvement*

1
2
3
4 201 Patients or the public were not involved in this research. However, the results of this
5
6
7 202 study will be disseminated to the public through various means including published
8
9
10 203 papers and presentations.
11
12 204
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

205 **Results**

206 *Study participants*

207 We analysed $n = 246\,671$ individuals in the baseline data set in FY2014 (Table1) and
208 $n = 181\,959$ individuals in the cohort data set FY2014-FY2018. Because follow-up was
209 four years, the cohort data set was slightly smaller than the baseline data set, especially
210 as a number of young individuals aged 20-24 and older individuals aged >60 dropped
211 out. This may be due to raising children or early retirement, and explains the higher
212 proportion of men in the cohort data set. Mean age and co-morbidity numbers among
213 CCI diseases were mostly comparable between the two data sets, although the
214 prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic
215 pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in
216 disease prevalence between genders were observed. Notably, men had a higher
217 prevalence of diabetes mellitus ($P = 0.001$) whereas women had a higher prevalence of
218 chronic pulmonary disease ($P = 0.002$).

219

220 *Estimated prevalence of multimorbidity in the Japanese total population*

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

1
2
3
4 223 estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population
5
6
7 224 (eTable 3A in the Supplement). The prevalence rate of multimorbidity increased with
8
9
10 225 age, i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39
11
12
13 226 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)),
14
15
16 227 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the
17
18
19 228 prevalence of diseases as well as below results are shown in eTable 3B in the
20
21
22 229 Supplement). Figure 2B shows the types of disease and their prevalence across age
23
24
25 230 groups. The top five diseases across the age groups “young” (20-39), “middle-age (40-
26
27
28 231 59), and “old” (60-74) in order of prevalence were “young”: chronic pulmonary disease,
29
30
31 232 peptic ulcer disease, liver disease, diabetes mellitus, and any malignancy; “middle-age”:
32
33
34 233 chronic pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and
35
36
37 234 any malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease,
38
39
40 235 peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up
41
42
43 236 across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is
44
45
46 237 shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-
47
48
49 238 44, the top five accelerating diseases were dementia, cerebrovascular disease,
50
51
52 239 peripheral vascular disease, metastatic tumour, and congestive heart failure.
53
54
55 240

1
2
3
4 241 The association of multimorbidity with outcome by age group.

5
6
7 242 Cox regression analysis showed that young individuals aged 20-39 with
8
9
10 243 multimorbidity had a higher hazard ratio (HR) compared to the same age group without
11
12
13 244 multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased across age
14
15
16 245 groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI, 3.23-3.53] ages
17
18
19 246 ≥ 60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of aging (HR =
20
21
22 247 1.62 [95% CI, 1.56-1.69] ages ≥ 60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59
23
24
25 248 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with multimorbidity
26
27
28 249 has a risk more than ages ≥ 60 without multimorbidity.

29
30
31 250 We also assessed HRs for non-multimorbid and multimorbid women and men
32
33
34 251 separately and found that women had a lower HR than men in the 20-39 age group but
35
36
37 252 a higher HR than men in the ≥ 60 age group (eTable 4 in the Supplement).
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

254 Discussion

255 In this study we analysed nationwide medical claims data for 15 chronic diseases in a
256 large cohort of the general population of Japan. As key findings, standardised
257 prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for
258 women. Further, age group-specific prevalence rates for multimorbidity ranged from
259 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an
260 accelerating increase after age 40. Importantly, significant differences in the clinical
261 outcomes of multimorbidity versus no multimorbidity were already present in young and
262 middle-aged individuals.

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

1
2
3
4 272 diseases associated with health-related quality of life loss. The presence of mental or
5
6
7 273 psychosomatic disorders, which have been shown to be increasing, particularly in
8
9
10 274 individuals already suffering from other chronic diseases,²⁷ younger people,²⁸ and
11
12
13 275 people with a low socio-economic status.²⁹ Such diseases often remain undiagnosed or
14
15
16 276 underreported in health records.³⁰ These limitations likely contributed to an
17
18
19 277 underestimation of multimorbidity in our cohort. Further, because we did not manually
20
21
22 278 verify the presence of disease using the physician's medical records data or medication
23
24
25 279 information, disease names extracted from the medical claims data might be incorrect in
26
27
28 280 some cases. In particular, Japanese physicians sometimes change the name of the
29
30
31 281 disease in the medical record to the "correct" disease name for the medication they wish
32
33
34 282 to prescribe, a practice called "disease name for claims data".
35
36
37 283 Because of differences in data sources and study populations, direct comparison of
38
39
40 284 population-based prevalence rates between studies is not straightforward. Nonetheless,
41
42
43 285 the standardised prevalence rates for multimorbidity as reported in the present study -
44
45
46 286 26.1% for men and 26.0% for women - are similar to those reported by recent studies in
47
48
49 287 other high-income countries, such as the United States (25% in men, 25% in women),³¹
50
51
52 288 England (24.4% in men, 30% in women),³² Canada (24.3% whole population),⁵ and
53
54
55 289 Denmark (19.3% in men, 23.7% in women).⁶ Also recently some Asian countries

1
2
3
4 290 reported similar prevalence, Iran (13.4% in men, 25.0% in women),³³ India, Bangladesh
5
6
7 291 (53.7% - 56.5% in both gender, over aged 60).³⁴ Many previous studies on
8
9
10 292 multimorbidity focused on the older generation, aged 65 and up, because of the larger
11
12
13 293 number of chronic diseases in this age group and the increasing number of people
14
15
16 294 entering it. However, our present data show that already approximately 10% of 30-34-,
17
18
19 295 19% of 45-49-, and 33% of 55-59-year-olds have ≥ 2 chronic diseases. Further, 1% of
20
21
22 296 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥ 5 chronic diseases. These
23
24
25 297 results show that multimorbidity is already prominent in the middle-aged population.
26
27
28 298 Recent studies reported similar or slightly higher prevalence rates for ≥ 2 chronic
29
30
31 299 diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)²⁹ and a
32
33
34 300 Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)⁵
35
36
37 301 population, although these two studies also included mental diseases and osteoporosis,
38
39
40 302 which our present study did not. Our present study shows that, among 15 chronic
41
42
43 303 diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease
44
45
46 304 (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer
47
48
49 305 disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes
50
51
52 306 mellitus, prevalence in the present study is similar to that previously reported in an
53
54
55 307 American population (15-30% in individuals aged 55-65)²⁹ but higher than that in a

1
2
3
4 308 Canadian population (16.6% in individuals aged 55-64)⁴. The prevalence of chronic
5
6
7 309 pulmonary disease in our present 55-65-year-olds was almost twice as high as those
8
9
10 310 seen for the combined prevalence of asthma and chronic obstructive pulmonary disease
11
12
13 311 (COPD) in an American population aged 55-65 years (5% for men and 10% for
14
15
16 312 women)²⁹ and in a Canadian population aged 55-64 years (13.7%).⁵ This difference
17
18
19 313 might have arisen due to our inclusion of various other pulmonary diseases besides
20
21
22 314 asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in
23
24
25 315 the present study was comparable to that seen in an adult population in Northern Italy³⁵
26
27
28 316 and in an adult population in Korea,³⁶ although this comparison requires care since the
29
30
31 317 types of liver disease in these studies and the age groups included vary.

32
33
34 318 Analysis of clinical outcomes using Cox regression revealed that the presence of
35
36
37 319 multimorbidity increased HRs in all age groups, including young individuals. In addition,
38
39
40 320 comparison of the increased HRs resulting from multimorbidity versus no multimorbidity
41
42
43 321 showed that the impact of multimorbidity exceeds that of increasing age. These results
44
45
46 322 indicate that multimorbidity places a burden on all age groups.

47
48
49 323 Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary
50
51
52 324 disease, liver disease, peptic ulcer disease, and any malignancy) in the present study
53
54
55 325 are lifestyle-related diseases that develop slowly over time. This trend should be
56
57
58
59
60

1
2
3
4 326 greeted with alarm. We trust that this study raises awareness of the potential health
5
6
7 327 risks and burden associated with the early onset of multimorbidity in young and middle-
8
9
10 328 age, the period when one is busy working and raising children. Future studies should
11
12
13 329 investigate the specific lifestyle factors associated with an elevated risk of multimorbidity
14
15
16 330 in the Japanese working population. Ultimately, public health care policies should be
17
18
19 331 aimed at efforts to reverse the trend toward early multimorbidity onset.
20
21

22 332 In conclusion, the present study revealed that the impact of multimorbidity is already
23
24
25 333 prominent in middle-aged Japanese, with elevated adverse events such as
26
27
28 334 hospitalisation or death. In addition, the risk posed by multimorbidity exceeds that of
29
30
31 335 aging in all age groups. These results underscore the need to undertake healthcare
32
33
34 336 intervention against the onset of multimorbidity before middle-age, and not to leave it as
35
36
37 337 a problem for geriatricians.
38
39

40 338

43 339 **Ethical Approval**

44
45
46 340 The present study was approved by the Institutional Review Board (IRB) of Kyoto
47
48
49 341 University (approval number: R0817). All data were anonymised before analysis and
50
51
52 342 none of the researchers had access to patient-identifiable information. The IRB waived
53
54
55 343 informed consent for this observational study.
56
57
58
59
60

1
2
3
4 3445
6
7 345 **Data Availability Statement**
89
10 346 All data are incorporated into the article and its online supplementary material.
11
1213 347
14
1516 348 **Author Contributions**
1718
19 349 Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors.
20
2122 350 Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important
23
2425 351 intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS.
26
2728 352 Administrative, technical, or material support: YS, SF. Study supervision: SF, AI, TN.
29
3031 353 YS had full access to all the data in the study and takes responsibility for the integrity of
32
3334 354 the data and the accuracy of the data analysis. All authors gave final approval and
35
3637 355 agreed to be accountable for all aspects of work.
38
3940 356
41
4243 357 **Acknowledgements**
4445
46 358 The authors are grateful to HIA²CE for providing data for the present study.
47
4849 359
50
5152 360 **Funding**
53
54
55
56
57
58
59
60

1
2
3
4 361 This work was supported by Grants-in-Aid from the Japan Society for the Promotion of
5
6
7 362 Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in
8
9
10 363 the design of the study; in the collection, analysis and interpretation of data; in the
11
12
13 364 writing of the report; or in the decision to submit the article for publication.
14
15

16 365

17
18
19 366 **Competing Interests**

20
21
22 367 None declared.
23
24

25 368

26
27
28 369 **Patient Consent for Publication**

29
30
31 370 Not applicable.
32
33

34 371

35
36
37 372

38
39
40 373 **Figure Legends**

41
42
43 374 **Figure 1.** Participant selection flowchart. FY; fiscal year
44
45

46 375

47
48
49 376 **Figure 2.** Multimorbidity across age groups in the Japanese total population aged 20-

50
51
52 377 74. **A)** Percentage of the population having 0 to ≥ 5 chronic diseases by age group. **B)**
53
54
55
56
57
58
59
60

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

380

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

384

385 **References**

- 386 1 Bleich SN, Sherrod C, Chiang A, *et al.* Systematic Review of Programs Treating
387 High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities
388 in the United States, 2008-2014. *Prev Chronic Dis.* Nov 12 2015;12:E197.
389 doi:10.5888/pcd12.150275
- 390 2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative
391 review. *Prev Med Rep.* Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008
- 392 3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y,
393 Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of
394 multimorbidity in a middle-income country. *PLoS One.* 2020;15(12):e0243614.
395 doi:10.1371/journal.pone.0243614
- 396 4 Low LL, Kwan YH, Ko MSM, *et al.* Epidemiologic Characteristics of Multimorbidity
397 and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging

- 1
2
3 398 Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245.
4
5
6 399 doi:10.1001/jamanetworkopen.2019.15245
7
8 400 5 Pefoyo AJ, Bronskill SE, Gruneir A, *et al*. The increasing burden and complexity of
9
10 401 multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-
11
12 402 1733-2
13
14
15 403 6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the
16
17 404 prevalence of multimorbidity - A register-based population study. *BMC Public*
18
19 405 *Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8
20
21
22 406 7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of
23
24 407 multimorbidity on healthcare utilisation and work productivity by socioeconomic
25
26 408 groups: Cross-sectional analyses of Australia and Japan. *PLoS One*.
27
28 409 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281
29
30
31 410 8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization
32
33 411 and costs in an elderly community-dwelling population: a claims data based
34
35 412 observational study. *BMC Health Serv Res*. Jan 22 2015;15:23.
36
37 413 doi:10.1186/s12913-015-0698-2
38
39
40 414 9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-
41
42 415 specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-
43
44 416 sectional study based on nationwide claims data. *BMJ Open*. Jun 9
45
46 417 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333
47
48
49 418 10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in
50
51 419 relation to age, gender and immigrant status: a cross-sectional study based on
52
53
54
55
56
57
58
59
60

- 1
2
3 420 administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812.
4
5
6 421 doi:10.1136/bmjopen-2016-012812
7
8 422 11 Picco L, Achilla E, Abdin E, *et al*. Economic burden of multimorbidity among older
9
10 423 adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10
11
12 424 2016;16:173. doi:10.1186/s12913-016-1421-7
13
14
15 425 12 van den Bussche H, Schon G, Kolonko T, *et al*. Patterns of ambulatory medical
16
17 426 care utilization in elderly patients with special reference to chronic diseases and
18
19 427 multimorbidity--results from a claims data based observational study in Germany.
20
21 428 *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54
22
23
24 429 13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of
25
26 430 risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a
27
28 431 longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152.
29
30 432 doi:10.1186/s12916-017-0913-6
31
32
33 433 14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising
34
35 434 burden of multimorbidity and related socio-demographic factors: a repeated
36
37 435 cross-sectional study of Ontarians. *Can J Public Health*. Apr 13
38
39 436 2021;doi:10.17269/s41997-021-00474-y
40
41
42 437 15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in
43
44 438 multimorbidity, complex multimorbidity and multiple functional limitations in the
45
46 439 ageing population of England, 2002-2015. *J Comorb*. Jan-Dec
47
48 440 2019;9:2235042X19872030. doi:10.1177/2235042X19872030
49
50
51 441 16 Katsutoshi H, Annabel B, Yasuhiko M, *et al*. Current Status, Challenges, and
52
53 442 Future Perspectives of Real-World Data and Real-World Evidence in Japan.
54
55
56
57
58
59
60

- 1
2
3 443 *Drugs - Real World Outcomes*. 2021;8:459–480. doi:org/10.1007/s40801-021-
4
5 444 00266-3
6
7
8 445 17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments
9
10 446 used for measuring the association of the level of multimorbidity and clinically
11
12 447 important outcomes. *BMJ Open*. 2021;May
13
14 448 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.
15
16
17 449 18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and
18
19 450 implications for health care, research, and medical education: a cross-sectional
20
21 451 study. *Lancet*. 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.
22
23
24 452 19 Mikk J, Heti P, Anneli U, et al. Prevalence of chronic conditions and multimorbidity
25
26 453 in Estonia: a population-based cross-sectional study. *BMJ Open*. 2021;Oct
27
28 454 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.
29
30
31 455 20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying
32
33 456 prognostic comorbidity in longitudinal studies: development and validation. *J*
34
35 457 *Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan
36
37 458 H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index
38
39 459 and score for risk adjustment in hospital discharge abstracts using data from 6
40
41 460 countries. *Am J Epidemiol*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433
42
43
44
45 461 21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative
46
47 462 Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*.
48
49 463 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 464 22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring
4
5
6 465 multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*.
7
8 466 Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098
9
10 467 23 Le Reste JY, Nabbe P, Manceau B, *et al*. The European General Practice
11
12 468 Research Network presents a comprehensive definition of multimorbidity in family
13
14 469 medicine and long term care, following a systematic review of relevant literature.
15
16
17 470 *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001
18
19 471 24 Ooba N, Setoguchi S, Ando T, *et al*. Claims-based definition of death in Japanese
20
21 472 claims database: validity and implications. *PLoS One*. 2013;8(5):e66116.
22
23
24 473 doi:10.1371/journal.pone.0066116
25
26 474 25 Sakai M, Ohtera S, Iwao T, *et al*. Validation of claims data to identify death among
27
28 475 aged persons utilizing enrollment data from health insurance unions. *Environ*
29
30
31 476 *Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3
32
33 477 26 Statistics Bureau of Japan. Preliminary count of the Japanese population.
34
35 478 Accessed March, 2014. <http://www.stat.go.jp/data/jinsui/index.html>
36
37
38 479 27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and
39
40 480 depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med*
41
42 481 *Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234
43
44
45 482 28 Egede LE. Major depression in individuals with chronic medical disorders:
46
47 483 prevalence, correlates and association with health resource utilization, lost
48
49 484 productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct
50
51 485 2007;29(5):409-16. doi:10.1016/j.genhosppsy.2007.06.002
52
53
54
55
56
57
58
59
60

- 1
2
3 486 29 Rocca WA, Boyd CM, Grossardt BR, *et al.* Prevalence of multimorbidity in a
4
5 487 geographically defined American population: patterns by age, sex, and
6
7 488 race/ethnicity. *Mayo Clin Proc.* Oct 2014;89(10):1336-49.
9
10 489 doi:10.1016/j.mayocp.2014.07.010
11
12 490 30 Cassell A, Edwards D, Harshfield A, *et al.* The epidemiology of multimorbidity in
13
14 491 primary care: a retrospective cohort study. *Br J Gen Pract.* Apr
15
16 492 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465
17
18
19 493 31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al.* Comparison of the
20
21 494 information provided by electronic health records data and a population health
22
23 495 survey to estimate prevalence of selected health conditions and multimorbidity.
24
25 496 *BMC Public Health.* Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251
26
27
28 497 32 St Sauver JL, Boyd CM, Grossardt BR, *et al.* Risk of developing multimorbidity
29
30 498 across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ*
31
32 499 *Open.* Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413
33
34
35 500 33 Masoomah A, Azam M, Mehdi Y. *et al.* Multimorbidity as an important issue among
36
37 501 women: results of a gender difference investigation in a large population-based
38
39 502 cross-sectional study in West Asia. *BMJ Open.* 2017;May 9;7(5):e013548. doi:
40
41 503 10.1136/bmjopen-2016-013548.
42
43
44 504 34 Sanghamitra P, Subhashisa S, Mohammad AH, *et al.* Prevalence and outcomes of
45
46 505 multimorbidity in South Asia: a systematic review *bmj open.* *BMJ Open.* 2015 Oct
47
48 506 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 507 35 Bellentani S, Tiribelli C, Saccoccio G, *et al.* Prevalence of chronic liver disease in
4
5 508 the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec
6
7 509 1994;20(6):1442-9. doi:10.1002/hep.1840200611
8
9

10 510 36 Park SH, Plank LD, Suk KT, *et al.* Trends in the prevalence of chronic liver
11
12 511 disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr
13
14 512 2020;26(2):209-215. doi:10.3350/cmh.2019.0065
15
16

17 513

18
19 514
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 515 **Supplementary Information**
4

5
6 516

7
8 517 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define

9
10 518 diseases in medical claims data

11
12 519 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and

13
14 520 cohort data

15
16
17 521 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied

18
19 522 to the Japanese total population by gender

20
21 523 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied

22
23 524 to the Japanese total population by age group

24
25
26 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on

27
28 hospitalisation or death rates in a 5-year cohort of $n = 111\ 088$ men and

29
30
31 $n = 70\ 871$ women. Cox regression analysis

32
33 525
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

526 **Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese**
 527 **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

528

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

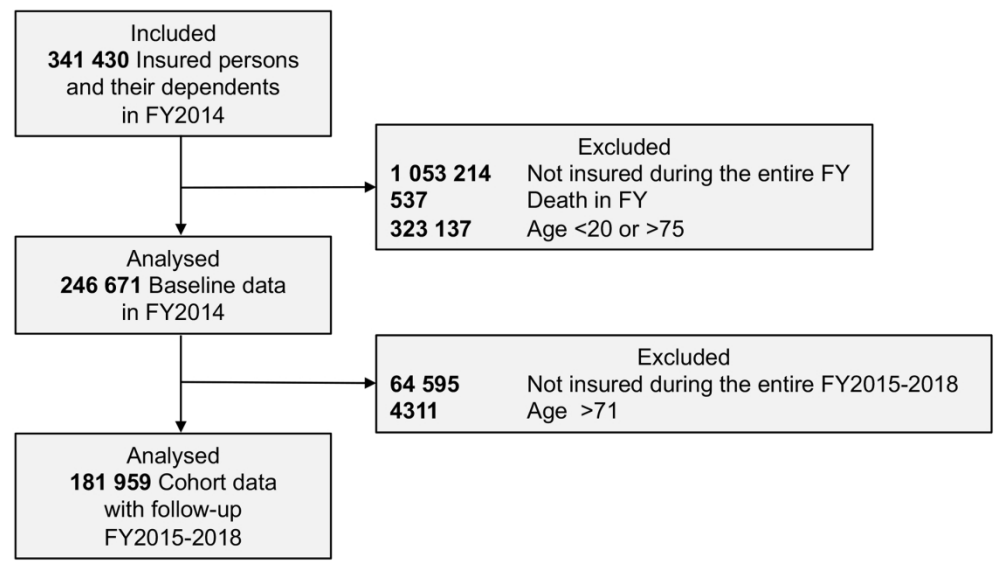


Figure 1. Participant selection flowchart. FY; fiscal year

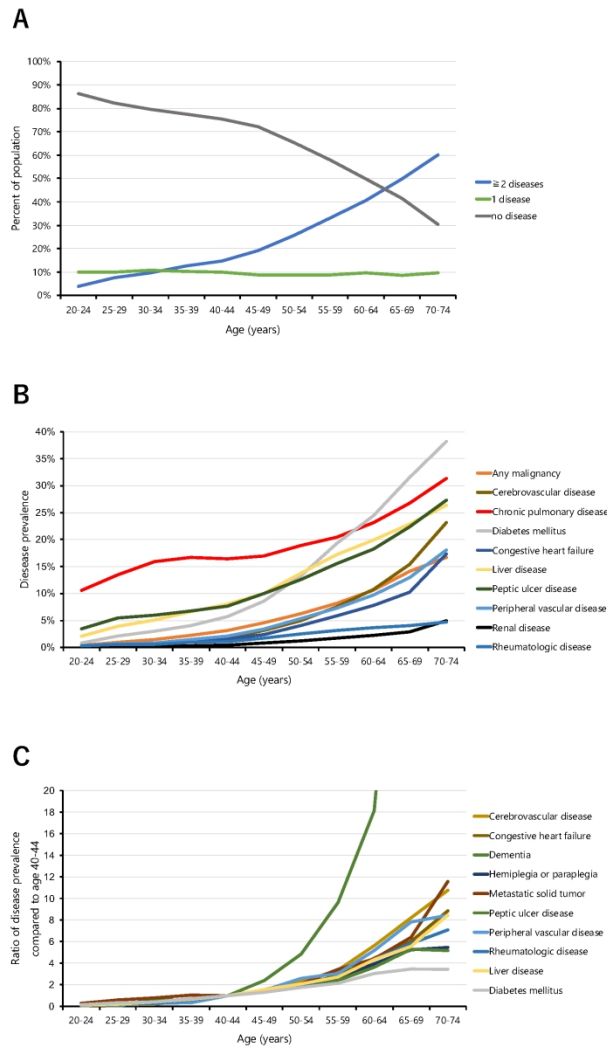


Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥ 2 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44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

297x420mm (200 x 200 DPI)

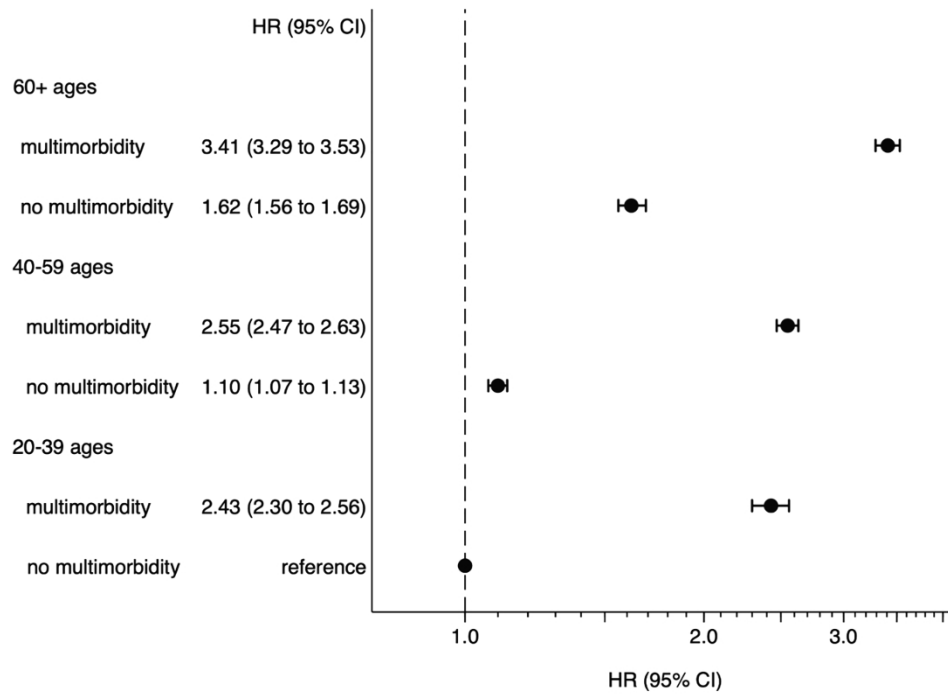


Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

1
2
3 Supplementary material
4
5

6 Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a
7 retrospective cohort study using nationwide medical claims data in the middle-aged generation
8
9

10
11 Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD
12
13

14
15
16 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define diseases in medical claims data
17

18 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and cohort data
19

20 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
21 by gender
22

23 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
24 by age group
25
26

27 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year
28 cohort of $n = 111\ 088$ men and $n = 70\ 871$ women. Cox regression analysis
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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-C41.x, 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

<i>N</i>	Baseline data in FY2014		Cohort data		<i>P</i> -value ^c
	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
<i>N</i>	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
^aAny malignancy includes leukemia and
lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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%)

^aAny 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%)

^aAny 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%)
---	------------	---------	-----------	---------	-----------	---------	-----------	---------

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

^aAny 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

^aReferences are female for sex, no disease for morbidity variables

^bReference 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 (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Suppl. Table 2 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 (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	16, Fig. 3
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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **1 Title**

5
6
7 2 The prevalence of multimorbidity and its associations with hospitalisation or death in
8
9
10 3 Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in
11
12
13 4 the middle-aged generation

14
15
16 **5 Authors**

17
18
19 6 Yoshiyuki Saito^{1,2*} PharmD, Ataru Igarashi^{1,3} PhD, Takeo Nakayama² MD PhD, Shingo
20
21
22 7 Fukuma⁴ MD

23
24
25
26
27
28 **9 Author Affiliations**

29
30
31 10 ¹Department of Health Economics & Outcomes Research, Graduate School of
32
33
34 11 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo
35
36
37 12 113-0033, Japan

38
39
40 13 ²Department of Health Informatics, School of Public Health, Graduate School of
41
42
43 14 Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

44
45
46 15 ³Unit of Public Health and Preventive Medicine, Yokohama City University School of
47
48
49 16 Medicine, Kanagawa 236-0027, Japan

50
51
52 17 ⁴School of Human Health Sciences, Graduate School of Medicine, Kyoto University,
53
54
55 18 Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

1
2
3
4 195
6
7 20 **Running head**8
9
10 21 The burden of multimorbidity in Japan 2014-201911
12
13 2214
15
16 23 ***Corresponding author**17
18
19 24 Yoshiyuki Saito, PharmD20
21
22 25 Department of Health Economics & Outcomes Research, Graduate School of23
24
25 26 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo26
27
28 27 113-0033, Japan29
30
31 28 E-mail: saito.yoshiyuki.86x@kyoto-u.jp32
33
34 29 Tel: +81-3-5841-482835
36
37 3038
39
40 31 Word count: 3669 (incl. abstract)41
42
43 32 Tables: 144
45
46 33 Figures: 347
48
49 34 Supplementary Tables: 450
51
52 3553
54
55 36

1
2
3
4 37 **Abstract**

5
6
7 38 **Objective**

8
9
10 39 To describe the prevalence of multimorbidity and its associations with clinical outcomes
11
12
13 40 across age groups.

14
15
16 41 **Design**

17
18
19 42 Retrospective cohort study using nationwide medical claims data.

20
21
22 43 **Setting**

23
24
25 44 Carried out in Japan between April 2014 and March 2019.

26
27
28 45 **Participants**

29
30
31 46 N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance
32
33
34 47 Association for Architecture and Civil Engineering companies (HIA²CE) were included
35
36
37 48 into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959 individuals
38
39
40 49 were included into the cohort data set spanning FY2014-FY2018.

41
42
43 50 **Exposures**

44
45
46 51 Multimorbidity was defined as having ≥ 2 of 15 chronic conditions according to the ICD-
47
48
49 52 10 codes of the Charlson Comorbidity Index.

50
51
52 53 **Primary and Secondary Outcomes**

1
2
3
4 54 Primary outcome for descriptive analysis: The standardised prevalence of multimorbidity
5
6
7 55 across age groups was evaluated using data from FY 2014 and extrapolated to the
8
9
10 56 Japanese total population. Secondary Outcome for Cox regression model:
11
12
13 57 Hospitalisation or death events were traced by month using medical claims data and
14
15
16 58 insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation
17
18
19 59 and/or death events across age groups were analysed using a Cox regression model.
20
21

22 60 **Results**

23
24
25 61 The standardised prevalence rate of multimorbidity in the nationwide Japanese total
26
27
28 62 population was approximately 5% (ages 25-24 (3.9%), 25-29 (7.7%)), 10% (30-34
29
30
31 63 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-
32
33
34 64 59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%),), and 60% (70-74).
35
36

37 65 Compared to individuals aged 20-39 without multimorbidity, those with multimorbidity
38
39
40 66 had a higher incidence of clinical events in any age group (HR = 2.43 [95% CI, 2.30-
41
42
43 67 2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and HR = 3.41 [95%
44
45
46 68 CI, 3.23-3.53] in ages ≥ 60). The difference in the incidence of clinical events between
47
48
49 69 multimorbidity and no-multimorbidity was larger than that between age groups.
50
51

52 70 **Conclusions**

1
2
3
4 71 Multimorbidity is already prevalent in the middle-aged generation and is associated with
5
6
7 72 poor clinical outcomes. These findings underscore the significance of multimorbidity and
8
9
10 73 highlight the urgent need for preventive intervention at the public health care level.
11
12

13 74
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4 75 **Article Summary**
5
6

7 76
8
9

10 77 Strengths and limitations of this study
11
12

- 13 78 • The current study covers a wide age range of individuals from a nationwide
14
15
16 79 general population.
17
18
19 80 • Japan`s high medical insurance coverage rate made it possible to
20
21
22 81 comprehensively identify chronic diseases from receipts.
23
24
25 82 • The longitudinal analysis enabled the examination of clinical outcomes of
26
27
28 83 multiple co-morbidities.
29
30
31 84 • The prevalence of multimorbidity may be underestimated because the target
32
33
34 85 population comprised regular employees and their families and might
35
36
37 86 accordingly be healthier than the general population.
38
39

40 87
41
42

43 88 **Keywords**
44
45

46 89 chronic disease, insurance claims, middle age, multimorbidity, preventive medicine
47
48
49 90
50
51
52
53
54
55
56
57
58
59
60

91 Introduction

92 Aging societies worldwide face the problem of how to provide adequate and
93 affordable health care for a growing number of patients with multiple chronic conditions,
94 termed multimorbidity.^{1,2} Managing multimorbidity is becoming a global challenge on the
95 clinical and public healthcare level not only in high-, but also in low- and middle-income
96 countries.³ Many epidemiological studies on multimorbidity have shown its association
97 with age, socio-demographic and socio-economic factors.⁴⁻⁷ In addition, numerous
98 studies have shown that multiple comorbidities are common in older people.⁸⁻¹¹ It has
99 been reported that multimorbid older patients had more than twice as many contacts per
100 year with physicians than those without multimorbidity¹² and that the likelihood of being
101 hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.⁸ On the
102 other hand, the accumulation of chronic diseases occurs continuously from middle age.
103 A number of recent studies conducted in various countries have reported that the onset
104 of multimorbidity is shifting towards younger age groups.^{6, 13-15} However, multimorbidity
105 studies tend to focus on older people, and in-depth knowledge on multimorbidity in
106 younger age groups is lacking.

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

1
2
3
4 109 cohort. Our findings add to existing knowledge by showing that multimorbidity has a
5
6
7 110 significant impact on health starting from middle age and underscore the need for
8
9
10 111 preventive intervention on the public health care level.
11

12 112
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

113 **Materials and Methods**

114 *Data source*

115 We used the nationwide medical claims and enrolment data of the Health Insurance
116 Association for Architecture and Civil Engineering companies (HIA²CE), which is one of
117 the largest social insurance associations in Japan. HIA²CE is a comprehensive insurer
118 which includes 1700 companies, from small engineering companies to middle and large
119 construction companies across Japan. This claims database covers a total of 400 000
120 insured persons, consisting of employees and their dependents.

121 The insured-based data base is used widely and one of the popular real-world data in
122 Japan.¹⁶ Japan has maintained a universal health coverage system since 1961. All
123 medical information regarding clinical practice covered by this health insurance is
124 included in the medical claims data, except for self-financed medical care and
125 individuals who receive public assistance. Furthermore, medical facilities have been
126 obliged since 2011 to submit medical claims data as an electronic record. Medical
127 claims data include the names of the diagnosed diseases, the names of medical
128 procedures, and the names of prescribed medications, among others. In the present
129 study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and
130 hospitalisations and deaths from the medical claims data in HIA²CE from FY2014 to

1
2
3
4 131 FY2018 (April 2014 to March 2019). The enrolment data from HIA²CE includes the
5
6
7 132 medical characteristics and in-out information of insured persons as of April 2019.
8
9

10 133

11
12
13 134 *Research design and study population*
14
15

16 135 We prepared two data sets for analysis. The first was a cross-sectional data set
17
18
19 136 containing baseline data of FY2014, which we used to describe the diagnosed disease
20
21
22 137 prevalence in FY2014. The study population for this baseline data set included
23
24
25 138 individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since
26
27
28 139 HIA²CE is a type of insurance for workers in Japan, the database include only under 75
29
30
31 140 years individuals. Therefore, the maximum age in this cohort was 74 years. Participants
32
33
34 141 younger than 20 in FY2014 as well as participants who died during FY2014 were
35
36
37 142 excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period,
38
39
40 143 FY2014 to FY2018 (April 2014 to March 2019). The second data set contained
41
42
43 144 participants insured in whole period. We used this cohort data set to conduct Cox
44
45
46 145 regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).
47
48

49 146

50
51
52 147 *Definition of diagnosed diseases and multimorbidity*
53
54
55
56
57
58
59
60

1
2
3
4 148 There are a variety of definitions for chronic conditions in multimorbidity studies.¹⁷⁻¹⁹
5
6
7 149 We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the
8
9
10 150 diseases associated with a significant risk of clinical events.²⁰ The reason, we used CCI,
11
12
13 151 was that we focused on describing the prevalence of each disease and also assessing
14
15
16 152 the association of multimorbidity on hospitalisation or death. The CCI Canadian version
17
18
19 153 has been reported to be applicable to Japanese claims data.²¹ We therefore defined
20
21
22 154 diagnosed diseases using medical claims data following ICD-10 codes of the CCI
23
24
25 155 Canada version. We merged the conditions “diabetes with chronic complication” and
26
27
28 156 “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease”
29
30
31 157 and “moderate or severe liver disease” into “liver disease”. The following 15 chronic
32
33
34 158 conditions were included: AIDS/HIV, any malignancy (including lymphoma and
35
36
37 159 leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart
38
39
40 160 failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour,
41
42
43 161 liver disease, myocardial infarction, peptic ulcer disease, renal disease, and
44
45
46 162 rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in
47
48
49 163 the Supplement. Multimorbidity status was defined as the concurrent presence of two or
50
51
52 164 more (≥ 2) diagnosed diseases among these conditions.^{22, 23} We only used confirmed
53
54
55 165 diagnoses, not including suspected diagnoses, in Japanese claims data.
56
57
58
59
60

1
2
3
4 1665
6
7 167 *Definition of outcome events; hospitalisation or death*
8
9

10 168 We defined two composite outcomes, hospitalisation or death, which occurred during
11
12
13 169 the period from FY2015 to FY2018. Using the medical claims data, both events were
14
15
16 170 traced by month. In Japan, the validity of death event information is reported to be less
17
18
19 171 sensitive if derived from medical claims data only.^{24, 25} Therefore, we also used death
20
21
22 172 information from enrolment data recorded by the insurer: if either contained death
23
24
25 173 information, this was defined as a death event.
26
27

28 174

30
31 175 *Estimation of diagnosed disease prevalence to a nationwide scale*
32
33

34 176 Diagnosed disease prevalence from baseline data was standardised to the
35
36
37 177 nationwide Japanese total population. We calculated prevalence rates according to
38
39
40 178 groups by 5-year age brackets and sex. Then, we estimated the prevalence rates
41
42
43 179 standardized to Japanese total population (age-sex standardized prevalence rate),
44
45
46 180 using the number from the vital statistics 2014 in Japan.²⁶
47
48

49 181

50
51
52 182 *The association of multimorbidity with outcome by age group*
53
54
55
56
57
58
59
60

1
2
3
4 183 To examine the association of multimorbidity with outcome by age group, we
5
6
7 184 performed Cox regression analysis adjusted by sex using cohort data from four
8
9
10 185 consecutive years (FY2015 to FY2018). The independent and additive effect of
11
12
13 186 multimorbidity and aging, we defined combined categories according to three age
14
15
16 187 groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥ 60 ,
17
18
19 188 respectively) and the binary status of multimorbidity, with the reference set as no
20
21
22 189 multimorbidity individuals aged 20-39. This model was able to show HR for aging alone
23
24
25 190 (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity
26
27
28 191 and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-
29
30
31 192 39 ages without multimorbidity).

193

194 *Statistical analysis*

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

1
2
3
4 201 generation. Results were considered statistically significant at a two-sided *P*-value of
5
6
7 202 less than 0.05. All analyses were conducted using Stata software version 15.1
8
9
10 203 (StataCorp LLC; College Station, TX, USA).
11
12

13 204
14
15

16 205 *Patient and Public involvement*

17

18
19 206 Patients or the public were not involved in this research. However, the results of this
20
21
22 207 study will be disseminated to the public through various means including published
23
24
25 208 papers and presentations.
26

27 209
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

210 **Results**

211 *Study participants*

212 We analysed $n = 246\,671$ individuals in the baseline data set in FY2014 (Table1) and
213 $n = 181\,959$ individuals in the cohort data set FY2014-FY2018. Because the follow-up
214 was four years, the cohort data set was slightly smaller than the baseline data set,
215 especially as a number of young individuals aged 20-24 and older individuals aged >60
216 dropped out. This may be due to raising children or early retirement, and explains the
217 higher proportion of men in the cohort data set. Mean age and co-morbidity numbers
218 among CCI diseases were mostly comparable between the two data sets, although the
219 prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic
220 pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in
221 disease prevalence between genders were observed. Notably, men had a higher
222 prevalence of diabetes mellitus ($P = 0.001$) whereas women had a higher prevalence of
223 chronic pulmonary disease ($P = 0.002$).

224

225 *Estimated prevalence of multimorbidity in the Japanese total population*

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

1
2
3
4 228 estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population
5
6
7 229 (eTable 3A in the Supplement). The prevalence rate with age was increased , i.e.,
8
9
10 230 approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)),
11
12
13 231 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64
14
15
16 232 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of
17
18
19 233 diseases as well as the below results are shown in eTable 3B in the Supplement).
20
21
22 234 Figure 2B shows the types of diseases and their prevalence across age groups. The top
23
24
25 235 five diseases across the age groups “young” (20-39), “middle-aged (40-59), and “old”
26
27
28 236 (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer
29
30
31 237 disease, liver disease, diabetes mellitus, and any malignancy; “middle-aged”: chronic
32
33
34 238 pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any
35
36
37 239 malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease,
38
39
40 240 peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up
41
42
43 241 across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is
44
45
46 242 shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-
47
48
49 243 44, the top five accelerating diseases were dementia, cerebrovascular disease,
50
51
52 244 peripheral vascular disease, metastatic tumour, and congestive heart failure.
53
54
55 245

1
2
3
4 246 The association of multimorbidity with outcome by age group.

5
6
7 247 The composite outcomes occurred 17.2% (death 0.8%, hospitalisation 16.9%) in the
8
9
10 248 follow-up period (eTable2). Cox regression analysis showed that young individuals aged
11
12
13 249 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age
14
15
16 250 group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased
17
18
19 251 across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI,
20
21
22 252 3.23-3.53] ages ≥ 60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of
23
24
25 253 aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥ 60 and HR = 1.10 [95% CI, 1.07-1.13] ages
26
27
28 254 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with
29
30
31 255 multimorbidity has a risk more than ages ≥ 60 without multimorbidity.

32
33
34 256 We also assessed HRs for non-multimorbid and multimorbid women and men
35
36
37 257 separately and found that women had a lower HR than men in the 20-39 age group but
38
39
40 258 a higher HR than men in the ≥ 60 age group (eTable 4 in the Supplement).
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

260 **Discussion**

261 In this study we analysed nationwide medical claims data for 15 chronic diseases in a
262 large cohort of the general population of Japan. As key findings, standardised
263 prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for
264 women. Further, age group-specific prevalence rates for multimorbidity ranged from
265 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an
266 accelerating increase after age 40. Importantly, significant differences in the clinical
267 outcomes of multimorbidity versus no multimorbidity were already present in young and
268 middle-aged individuals.

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

1
2
3
4 278 diseases associated with health-related quality of life loss. CCI originally includes
5
6
7 279 comorbidities that have a strong impact on mortality, not quality of life and well-being.
8
9
10 280 The presence of mental or psychosomatic disorders, which have been shown to be
11
12
13 281 increasing, particularly in individuals already suffering from other chronic diseases,²⁷
14
15
16 282 younger people,²⁸ and people with a low socio-economic status.²⁹ Such diseases often
17
18
19 283 remain undiagnosed or underreported in health records.³⁰ Also, we collected diseases
20
21
22 284 which were occurred during the year (FY2014). Therefore, patients who were untreated,
23
24
25 285 undiagnosed, or discontinued treatment cannot be picked up. These limitations likely
26
27
28 286 contributed to an underestimation of multimorbidity in our cohort. Further, because we
29
30
31 287 did not manually verify the presence of disease using the physician's medical records
32
33
34 288 data or medication information, disease names extracted from the medical claims data
35
36
37 289 might be incorrect in some cases. In particular, Japanese physicians sometimes change
38
39
40 290 the name of the disease in the medical record to the "correct" disease name for the
41
42
43 291 medication they wish to prescribe, a practice called "disease name for claims data".
44
45
46 292 Because of differences in data sources and study populations, direct comparison of
47
48
49 293 population-based prevalence rates between studies is not straightforward. Nonetheless,
50
51
52 294 the standardised prevalence rates for multimorbidity as reported in the present study -
53
54
55 295 26.1% for men and 26.0% for women - are similar to those reported by recent studies in
56
57
58
59
60

1
2
3
4 296 other high-income countries, such as the United States (25% in men, 25% in women),³¹
5
6
7 297 England (24.4% in men, 30% in women),³² Canada (24.3% whole population),⁵ and
8
9
10 298 Denmark (19.3% in men, 23.7% in women).⁶ Also recently some Asian countries
11
12
13 299 reported similar prevalence, Iran (13.4% in men, 25.0% in women),³³ India, and
14
15
16 300 Bangladesh (53.7% - 56.5% in both genders, over aged 60).³⁴ Many previous studies on
17
18
19 301 multimorbidity focused on the older generation, aged 65 and up, because of the larger
20
21
22 302 number of chronic diseases in this age group and the increasing number of people
23
24
25 303 entering it. However, our present data show that already approximately 10% of 30-34-,
26
27
28 304 19% of 45-49-, and 33% of 55-59-year-olds have ≥ 2 chronic diseases. Further, 1% of
29
30
31 305 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥ 5 chronic diseases. These
32
33
34 306 results show that multimorbidity is already prominent in the middle-aged population.
35
36
37 307 Recent studies reported similar or slightly higher prevalence rates for ≥ 2 chronic
38
39
40 308 diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)²⁹ and a
41
42
43 309 Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)⁵
44
45
46 310 population, although these two studies also included mental diseases and osteoporosis,
47
48
49 311 which our present study did not. Our present study shows that, among 15 chronic
50
51
52 312 diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease
53
54
55 313 (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer
56
57
58
59
60

1
2
3
4 314 disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes
5
6
7 315 mellitus, the prevalence in the present study is similar to that previously reported in an
8
9
10 316 American population (15-30% in individuals aged 55-65)²⁹ but higher than that in a
11
12
13 317 Canadian population (16.6% in individuals aged 55-64)⁴. The prevalence of chronic
14
15
16 318 pulmonary disease in our present 55-65-year-olds was almost twice as high as those
17
18
19 319 seen for the combined prevalence of asthma and chronic obstructive pulmonary disease
20
21
22 320 (COPD) in an American population aged 55-65 years (5% for men and 10% for
23
24
25 321 women)²⁹ and in a Canadian population aged 55-64 years (13.7%).⁵ This difference
26
27
28 322 might have arisen due to our inclusion of various other pulmonary diseases besides
29
30
31 323 asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in
32
33
34 324 the present study was comparable to that seen in an adult population in Northern Italy³⁵
35
36
37 325 and in an adult population in Korea,³⁶ although this comparison requires care since the
38
39
40 326 types of liver disease in these studies and the age groups included vary.

41
42
43 327 Analysis of clinical outcomes using Cox regression revealed that the presence of
44
45
46 328 multimorbidity increased HRs in all age groups, including young individuals. In addition,
47
48
49 329 the comparison of the increased HRs resulting from multimorbidity versus no
50
51
52 330 multimorbidity showed that the impact of multimorbidity exceeds that of increasing age.
53
54
55 331 These results indicate that multimorbidity places a burden on all age groups.

1
2
3
4 332 Most of the five most prevalent diseases (diabetes mellitus, chronic pulmonary
5
6
7 333 disease, liver disease, peptic ulcer disease, and any malignancy) in the present study
8
9
10 334 are lifestyle-related diseases that develop slowly over time. This trend should be
11
12
13 335 greeted with alarm. We trust that this study raises awareness of the potential health
14
15
16 336 risks and burden associated with the early onset of multimorbidity in young and middle-
17
18
19 337 aged, the period when one is busy working and raising children. Future studies should
20
21
22 338 investigate the specific lifestyle factors associated with an elevated risk of multimorbidity
23
24
25 339 in the Japanese working population. Ultimately, public health care policies should be
26
27
28 340 aimed at efforts to reverse the trend toward early multimorbidity onset.

31 341 In conclusion, the present study confirmed the prevalence of MM by including in the
32
33
34 342 denominator those who did not have the receipt of medical claims and to estimate the
35
36
37 343 prevalence of MM in the general population. Furthermore, we revealed that the impact
38
39
40 344 of multimorbidity is already clinically significant in middle-aged Japanese, with elevated
41
42
43 345 adverse events such as hospitalisation or death. In addition, the risk posed by
44
45
46 346 multimorbidity exceeds that of aging in all age groups. These results underscore the
47
48
49 347 need to undertake healthcare intervention against the onset of multimorbidity before
50
51
52 348 middle-aged, and not to leave it as a problem for geriatricians.

53
54
55 349

350 **Ethical Approval**

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

356 **Data Availability Statement**

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

359 **Author Contributions**

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

367

1
2
3
4 368 **Acknowledgements**

5
6
7 369 The authors are grateful to HIA²CE for providing data for the present study.
8
9

10 370

11
12
13 371 **Funding**

14
15
16 372 This work was supported by Grants-in-Aid from the Japan Society for the Promotion of

17
18
19 373 Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in

20
21
22 374 the design of the study; in the collection, analysis and interpretation of data; in the

23
24
25 375 writing of the report; or in the decision to submit the article for publication.
26
27

28 376

29
30
31 377 **Competing Interests**

32
33
34 378 None declared.
35
36

37 379

38
39
40 380 **Patient Consent for Publication**

41
42
43 381 Not applicable.
44
45

46 382

47
48
49 383

50
51
52 384 **Figure Legends**

53
54
55 385 **Figure 1.** Participant selection flowchart. FY; fiscal year
56
57
58

386

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

391

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

395

396 **References**

- 397 1 Bleich SN, Sherrod C, Chiang A, *et al.* Systematic Review of Programs Treating
398 High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities
399 in the United States, 2008-2014. *Prev Chronic Dis.* Nov 12 2015;12:E197.
400 doi:10.5888/pcd12.150275
- 401 2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative
402 review. *Prev Med Rep.* Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008
- 403 3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y,
404 Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of

- 1
2
3 405 multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614.
4
5 406 doi:10.1371/journal.pone.0243614
6
7
8 407 4 Low LL, Kwan YH, Ko MSM, *et al*. Epidemiologic Characteristics of Multimorbidity
9
10 408 and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging
11
12 409 Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245.
13
14 410 doi:10.1001/jamanetworkopen.2019.15245
15
16
17 411 5 Pefoyo AJ, Bronskill SE, Gruneir A, *et al*. The increasing burden and complexity of
18
19 412 multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-
20
21 413 1733-2
22
23
24 414 6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the
25
26 415 prevalence of multimorbidity - A register-based population study. *BMC Public*
27
28 416 *Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8
29
30
31 417 7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of
32
33 418 multimorbidity on healthcare utilisation and work productivity by socioeconomic
34
35 419 groups: Cross-sectional analyses of Australia and Japan. *PLoS One*.
36
37 420 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281
38
39
40 421 8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization
41
42 422 and costs in an elderly community-dwelling population: a claims data based
43
44 423 observational study. *BMC Health Serv Res*. Jan 22 2015;15:23.
45
46 424 doi:10.1186/s12913-015-0698-2
47
48
49 425 9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-
50
51 426 specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-
52
53
54
55
56
57
58
59
60

- 1
2
3 427 sectional study based on nationwide claims data. *BMJ Open*. Jun 9
4
5
6 428 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333
7
8 429 10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in
9
10 430 relation to age, gender and immigrant status: a cross-sectional study based on
11
12 431 administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812.
13
14 432 doi:10.1136/bmjopen-2016-012812
15
16
17 433 11 Picco L, Achilla E, Abdin E, *et al*. Economic burden of multimorbidity among older
18
19 434 adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10
20
21 435 2016;16:173. doi:10.1186/s12913-016-1421-7
22
23
24 436 12 van den Bussche H, Schon G, Kolonko T, *et al*. Patterns of ambulatory medical
25
26 437 care utilization in elderly patients with special reference to chronic diseases and
27
28 438 multimorbidity--results from a claims data based observational study in Germany.
29
30 439 *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54
31
32
33 440 13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of
34
35 441 risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a
36
37 442 longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152.
38
39 443 doi:10.1186/s12916-017-0913-6
40
41
42 444 14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising
43
44 445 burden of multimorbidity and related socio-demographic factors: a repeated
45
46 446 cross-sectional study of Ontarians. *Can J Public Health*. Apr 13
47
48 447 2021;doi:10.17269/s41997-021-00474-y
49
50
51 448 15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in
52
53 449 multimorbidity, complex multimorbidity and multiple functional limitations in the
54
55
56
57
58
59
60

- 1
2
3 450 ageing population of England, 2002-2015. *J Comorb.* Jan-Dec
4
5 451 2019;9:2235042X19872030. doi:10.1177/2235042X19872030
6
7
8 452 16 Katsutoshi H, Annabel B, Yasuhiko M, et al. Current Status, Challenges, and
9
10 453 Future Perspectives of Real-World Data and Real-World Evidence in Japan.
11
12 454 *Drugs - Real World Outcomes.* 2021;8:459–480. doi:org/10.1007/s40801-021-
13
14 455 00266-3
15
16
17 456 17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments
18
19 457 used for measuring the association of the level of multimorbidity and clinically
20
21 458 important outcomes. *BMJ Open.* 2021;May
22
23 459 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.
24
25
26 460 18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and
27
28 461 implications for health care, research, and medical education: a cross-sectional
29
30 462 study. *Lancet.* 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.
31
32
33 463 19 Jürisson M, Heti P, Anneli U, et al. Prevalence of chronic conditions and
34
35 464 multimorbidity in Estonia: a population-based cross-sectional study. *BMJ Open.*
36
37 465 2021;Oct 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.
38
39
40 466 20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying
41
42 467 prognostic comorbidity in longitudinal studies: development and validation. *J*
43
44 468 *Chronic Dis.* 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan
45
46 469 H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index
47
48 470 and score for risk adjustment in hospital discharge abstracts using data from 6
49
50 471 countries. *Am J Epidemiol.* Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433
51
52
53
54
55
56
57
58
59
60

- 1
2
3 472 21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative
4
5 Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*.
6 473
7 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.
8 474
9
- 10 475 22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring
11
12 multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*.
13 476
14 Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098
15 477
16
- 17 478 23 Le Reste JY, Nabbe P, Manceau B, *et al*. The European General Practice
18
19 Research Network presents a comprehensive definition of multimorbidity in family
20 479
21 medicine and long term care, following a systematic review of relevant literature.
22 480
23 *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001
24 481
25
- 26 482 24 Ooba N, Setoguchi S, Ando T, *et al*. Claims-based definition of death in Japanese
27
28 claims database: validity and implications. *PLoS One*. 2013;8(5):e66116.
29 483
30 doi:10.1371/journal.pone.0066116
31 484
32
- 33 485 25 Sakai M, Ohtera S, Iwao T, *et al*. Validation of claims data to identify death among
34
35 aged persons utilizing enrollment data from health insurance unions. *Environ*
36 486
37 *Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3
38 487
39
- 40 488 26 Statistics Bureau of Japan. Preliminary count of the Japanese population.
41
42 Accessed March, 2014. <http://www.stat.go.jp/data/jinsui/index.html>
43 489
44
- 45 490 27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and
46
47 depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med*
48
49 *Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234
50 492
51
- 52 493 28 Egede LE. Major depression in individuals with chronic medical disorders:
53
54 prevalence, correlates and association with health resource utilization, lost
55
56
57
58
59
60

- 1
2
3 495 productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct
4
5 496 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002
6
7
8 497 29 Rocca WA, Boyd CM, Grossardt BR, *et al*. Prevalence of multimorbidity in a
9
10 498 geographically defined American population: patterns by age, sex, and
11
12 499 race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49.
13
14 500 doi:10.1016/j.mayocp.2014.07.010
15
16
17 501 30 Cassell A, Edwards D, Harshfield A, *et al*. The epidemiology of multimorbidity in
18
19 502 primary care: a retrospective cohort study. *Br J Gen Pract*. Apr
20
21 503 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465
22
23
24 504 31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al*. Comparison of the
25
26 505 information provided by electronic health records data and a population health
27
28 506 survey to estimate prevalence of selected health conditions and multimorbidity.
29
30 507 *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251
31
32
33 508 32 St Sauver JL, Boyd CM, Grossardt BR, *et al*. Risk of developing multimorbidity
34
35 509 across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ*
36
37 510 *Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413
38
39
40 511 33 Masoomeh A, Azam M, Mehdi Y. *et al*. Multimorbidity as an important issue among
41
42 512 women: results of a gender difference investigation in a large population-based
43
44 513 cross-sectional study in West Asia. *BMJ Open*. 2017;May 9;7(5):e013548. doi:
45
46 514 10.1136/bmjopen-2016-013548.
47
48
49 515 34 Sanghamitra P, Subhashisa S, Mohammad AH, *et al*. Prevalence and outcomes of
50
51 516 multimorbidity in South Asia: a systematic review *bmj open*. *BMJ Open*. 2015 Oct
52
53 517 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.
54
55
56
57
58
59
60

1
2
3 518 35 Bellentani S, Tiribelli C, Saccoccio G, *et al.* Prevalence of chronic liver disease in
4
5
6 519 the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec
7
8 520 1994;20(6):1442-9. doi:10.1002/hep.1840200611
9

10 521 36 Park SH, Plank LD, Suk KT, *et al.* Trends in the prevalence of chronic liver
11
12 522 disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr
13
14 523 2020;26(2):209-215. doi:10.3350/cmh.2019.0065
15
16

17 524

18
19 525
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 526 **Supplementary Information**
4

5
6 527
7

8 528 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define
9
10 529 diseases in medical claims data
11

12 530 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and
13
14 531 cohort data
15

16
17 532 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied
18
19 533 to the Japanese total population by gender
20

21 534 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied
22
23 535 to the Japanese total population by age group
24

25
26 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on
27
28 hospitalisation or death rates in a 5-year cohort of $n = 111\ 088$ men and
29
30 $n = 70\ 871$ women. Cox regression analysis
31
32

33 536
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

537 **Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese**
 538 **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

539

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

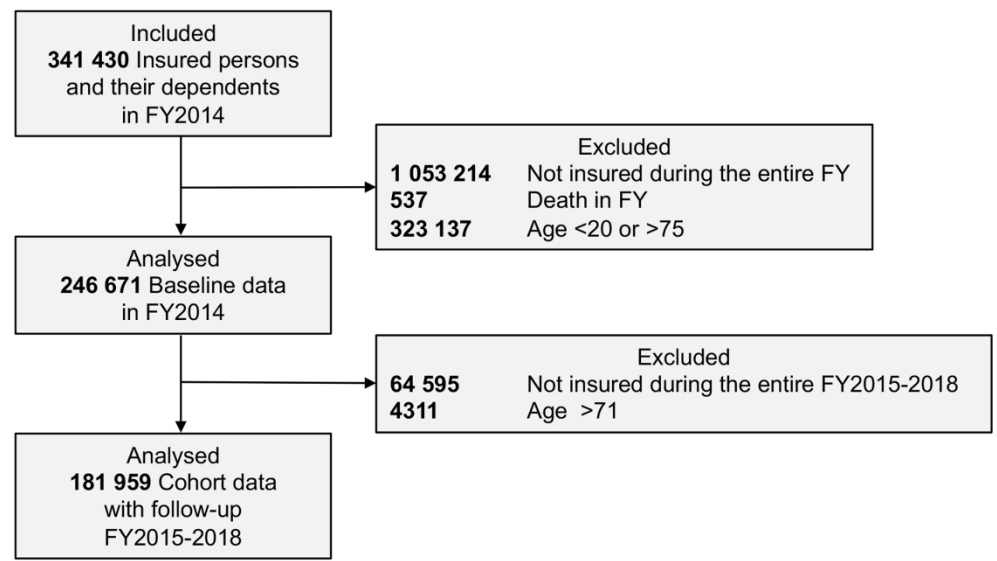


Figure 1. Participant selection flowchart. FY; fiscal year

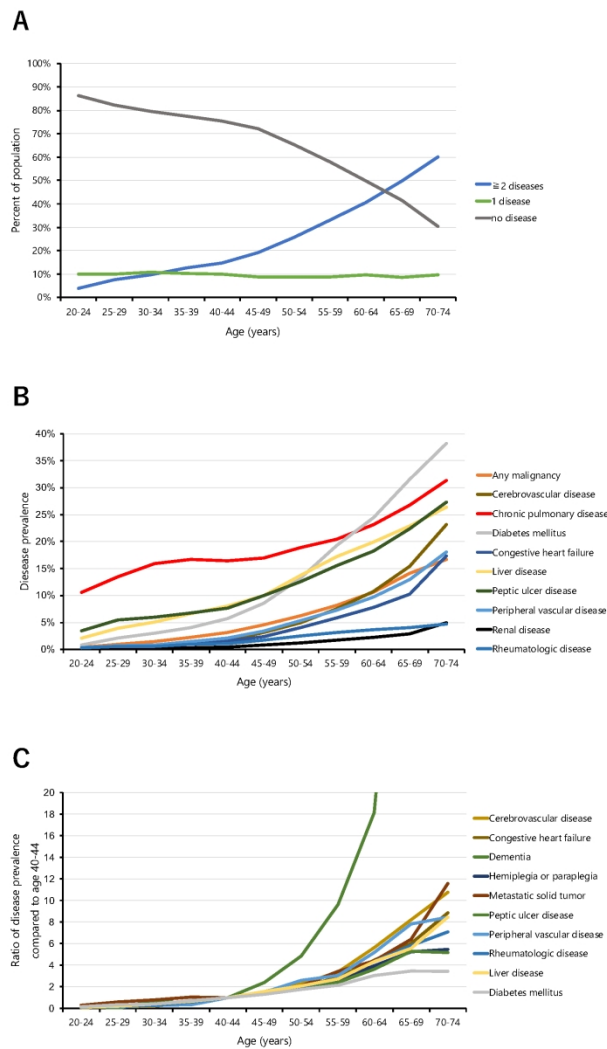


Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥ 2 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44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

297x420mm (200 x 200 DPI)

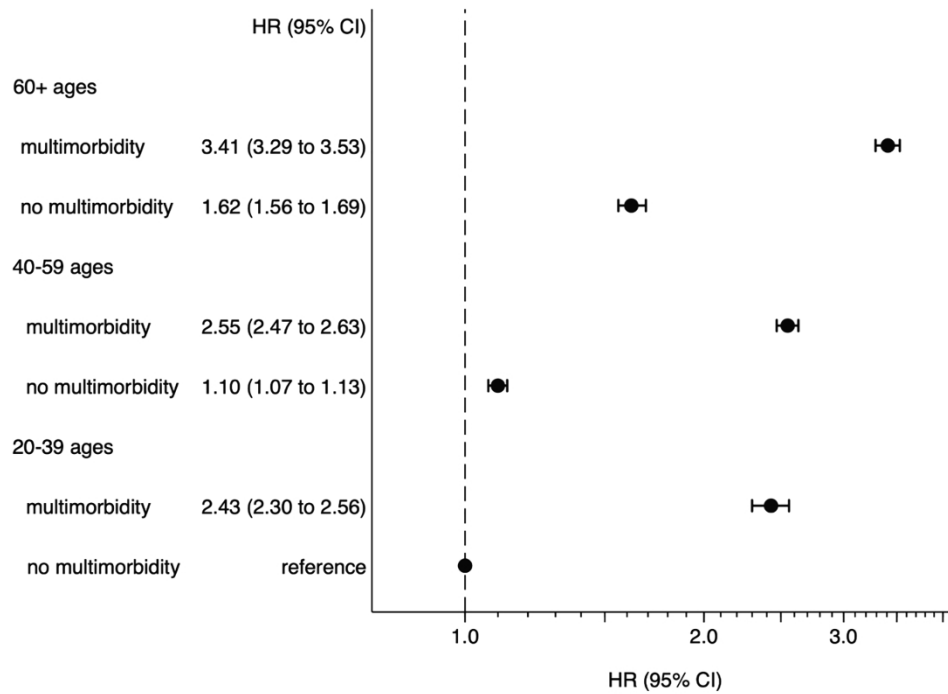


Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

1
2
3 Supplementary material
4
5

6 Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a
7 retrospective cohort study using nationwide medical claims data in the middle-aged generation
8
9

10
11 Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD
12
13

14
15
16 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define diseases in medical claims data
17

18 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and cohort data
19

20 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
21 by gender
22

23 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
24 by age group
25
26

27 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year
28 cohort of $n = 111\ 088$ men and $n = 70\ 871$ women. Cox regression analysis
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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-C41.x, 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

<i>N</i>	Baseline data in FY2014		Cohort data		<i>P</i> -value ^c
	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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
<i>N</i>	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 Disease no. among CCI	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
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
^aAny malignancy includes leukemia and
lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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%)

^aAny 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%)

^aAny 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%)
---	------------	---------	-----------	---------	-----------	---------	-----------	---------

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

^aAny 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

^aReferences are female for sex, no disease for morbidity variables

^bReference 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 (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Suppl. Table 2 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 (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	16, Fig. 3
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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **1 Title**

5
6
7 2 The prevalence of multimorbidity and its associations with hospitalisation or death in
8
9
10 3 Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in
11
12
13 4 the middle-aged generation

14
15
16 **5 Authors**

17
18
19 6 Yoshiyuki Saito^{1,2*} PharmD, Ataru Igarashi^{1,3} PhD, Takeo Nakayama² MD PhD, Shingo
20
21
22 7 Fukuma⁴ MD
23
24

25
26
27
28 **9 Author Affiliations**

29
30
31 10 ¹Department of Health Economics & Outcomes Research, Graduate School of
32
33
34 11 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo
35
36
37 12 113-0033, Japan

38
39
40 13 ²Department of Health Informatics, School of Public Health, Graduate School of
41
42
43 14 Medicine, Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

44
45
46 15 ³Unit of Public Health and Preventive Medicine, Yokohama City University School of
47
48
49 16 Medicine, Kanagawa 236-0027, Japan

50
51
52 17 ⁴School of Human Health Sciences, Graduate School of Medicine, Kyoto University,
53
54
55 18 Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan
56
57
58
59
60

1
2
3
4 195
6
7 20 **Running head**8
9
10 21 The burden of multimorbidity in Japan 2014-201911
12
13 2214
15
16 23 ***Corresponding author**17
18
19 24 Yoshiyuki Saito, PharmD20
21
22 25 Department of Health Economics & Outcomes Research, Graduate School of23
24
25 26 Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo26
27
28 27 113-0033, Japan29
30
31 28 E-mail: saito.yoshiyuki.86x@kyoto-u.jp32
33
34 29 Tel: +81-3-5841-482835
36
37 3038
39
40 31 Word count: 3638 (incl. abstract)41
42
43 32 Tables: 144
45
46 33 Figures: 347
48
49 34 Supplementary Tables: 450
51
52 3553
54
55 36

1
2
3
4 37 **Abstract**

5
6
7 38 **Objective**

8
9
10 39 To describe the prevalence of multimorbidity and its associations with clinical outcomes
11
12
13 40 across age groups.

14
15
16 41 **Design**

17
18
19 42 Retrospective cohort study using nationwide medical claims data.

20
21
22 43 **Setting**

23
24
25 44 Carried out in Japan between April 2014 and March 2019.

26
27
28 45 **Participants**

29
30
31 46 N = 246 671 Japanese individuals aged 20-74 enrolled in the Health Insurance were
32
33
34 47 included into the baseline data set for fiscal year (FY) 2014. Of those, N = 181 959
35
36
37 48 individuals were included into the cohort data set spanning FY2014-FY2018.

38
39
40 49 **Exposures**

41
42
43 50 Multimorbidity was defined as having ≥ 2 of 15 chronic conditions according to the ICD-
44
45
46 51 10 codes of the Charlson Comorbidity Index.

47
48
49 52 **Primary and Secondary Outcomes**

50
51
52 53 Primary outcome: The standardised prevalence of multimorbidity across age groups
53
54
55 54 was evaluated using data from FY 2014 and extrapolated to the Japanese total

1
2
3
4 55 population. Secondary Outcome: Hospitalisation or death events were traced by month
5
6
7 56 using medical claims data and insurer enrolment data. Associations between
8
9
10 57 multimorbidity and 5-year hospitalisation and/or death events across age groups were
11
12
13 58 analysed using a Cox regression model.
14
15

16 59 **Results**

17
18
19 60 The standardised prevalence rate of multimorbidity in the nationwide Japanese total
20
21
22 61 population was estimated to 26.1%. The prevalence rate with age was increased,
23
24
25 62 approximately 5%(ages 20-29), 10%(30-39), 20%(40-49), 30%(50-59), 50%(60-69), and
26
27
28 63 60%(70-74). Compared to individuals aged 20-39 without multimorbidity, those with
29
30
31 64 multimorbidity had a higher incidence of clinical events in any age group(HR = 2.43
32
33
34 65 [95% CI, 2.30-2.56] in ages 20-39, HR = 2.55 [95% CI, 2.47-2.63] in ages 40-59, and
35
36
37 66 HR = 3.41[95% CI, 3.23-3.53] in ages ≥ 60). The difference in the incidence of clinical
38
39
40 67 events between multimorbidity and no-multimorbidity was larger than that between age
41
42
43 68 groups.
44
45

46 69 **Conclusions**

47
48
49 70 Multimorbidity is already prevalent in the middle-aged generation and is associated with
50
51
52 71 poor clinical outcomes. These findings underscore the significance of multimorbidity and
53
54
55 72 highlight the urgent need for preventive intervention at the public health care level.
56
57
58
59
60

1
2
3
4 73 **Article Summary**
5
6

7 74
8
9

10 75 Strengths and limitations of this study
11
12

- 13 76 • The current study covers a wide age range of individuals from a nationwide
14
15
16 77 general population.
17
18
19 78 • Japan`s high medical insurance coverage rate made it possible to
20
21
22 79 comprehensively identify chronic diseases from receipts.
23
24
25 80 • The longitudinal analysis enabled the examination of clinical outcomes of
26
27
28 81 multiple co-morbidities.
29
30
31 82 • The prevalence of multimorbidity may be underestimated because the target
32
33
34 83 population comprised regular employees and their families and might
35
36
37 84 accordingly be healthier than the general population.
38
39
40
41
42

43 86 **Keywords**
44
45

46 87 chronic disease, insurance claims, middle age, multimorbidity, preventive medicine
47
48
49 88
50
51
52
53
54
55
56
57
58
59
60

89 Introduction

90 Aging societies worldwide face the problem of how to provide adequate and
91 affordable health care for a growing number of patients with multiple chronic conditions,
92 termed multimorbidity.^{1,2} Managing multimorbidity is becoming a global challenge on the
93 clinical and public healthcare level not only in high-, but also in low- and middle-income
94 countries.³ Many epidemiological studies on multimorbidity have shown its association
95 with age, socio-demographic and socio-economic factors.⁴⁻⁷ In addition, numerous
96 studies have shown that multiple comorbidities are common in older people.⁸⁻¹¹ It has
97 been reported that multimorbid older patients had more than twice as many contacts per
98 year with physicians than those without multimorbidity¹² and that the likelihood of being
99 hospitalised was increased by a factor of 5.6 due to multiple co-morbidities.⁸ On the
100 other hand, the accumulation of chronic diseases occurs continuously from middle age.
101 A number of recent studies conducted in various countries have reported that the onset
102 of multimorbidity is shifting toward younger age groups.^{6, 13-15} However, multimorbidity
103 studies tend to focus on older people, and in-depth knowledge on multimorbidity in
104 younger age groups is lacking.

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

1
2
3
4 107 cohort. Our findings add to existing knowledge by showing that multimorbidity has a
5
6
7 108 significant impact on health starting from middle age and underscore the need for
8
9
10 109 preventive intervention on the public health care level.
11

12
13 110
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

111 **Materials and Methods**

112 *Data source*

113 We used the nationwide medical claims and enrolment data of the Health Insurance
114 Association for Architecture and Civil Engineering companies (HIA²CE), which is one of
115 the largest social insurance associations in Japan. HIA²CE is a comprehensive insurer
116 which includes 1700 companies, from small engineering companies to middle and large
117 construction companies across Japan. This claims database covers a total of 400 000
118 insured persons, consisting of employees and their dependents.

119 The insured-based database is used widely and one of the popular real-world data in
120 Japan.¹⁶ Japan has maintained a universal health coverage system since 1961. All
121 medical information regarding clinical practice covered by this health insurance is
122 included in the medical claims data, except for self-financed medical care and
123 individuals who receive public assistance. Furthermore, medical facilities have been
124 obliged since 2011 to submit medical claims data as an electronic record. Medical
125 claims data include the names of the diagnosed diseases, the names of medical
126 procedures, and the names of prescribed medications, among others. In the present
127 study, we extracted the age, sex, names and ICD-10 codes of diagnosed diseases, and
128 hospitalisations and deaths from the medical claims data in HIA²CE from FY2014 to

1
2
3
4 129 FY2018 (April 2014 to March 2019). The enrolment data from HIA²CE includes the
5
6
7 130 medical characteristics and in-out information of insured persons as of April 2019.
8
9

10 131

13 132 *Research design and study population*

16 133 We prepared two data sets for analysis. The first was a cross-sectional data set
17
18
19 134 containing baseline data of FY2014, which we used to describe the diagnosed disease
20
21
22 135 prevalence in FY2014. The study population for this baseline data set included
23
24
25 136 individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since
26
27
28 137 HIA²CE is a type of insurance for workers in Japan, the database include only under 75
29
30
31 138 years individuals. Therefore, the maximum age in this cohort was 74 years. Participants
32
33
34 139 younger than 20 in FY2014 as well as participants who died during FY2014 were
35
36
37 140 excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period,
38
39
40 141 FY2014 to FY2018 (April 2014 to March 2019). The second data set contained
41
42
43 142 participants insured in whole period. We used this cohort data set to conduct Cox
44
45
46 143 regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).
47
48

49 144

52 145 *Definition of diagnosed diseases and multimorbidity*

1
2
3
4 146 There are a variety of definitions for chronic conditions in multimorbidity studies.¹⁷⁻¹⁹
5
6
7 147 We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the
8
9
10 148 diseases associated with a significant risk of clinical events.²⁰ The reason, we used CCI,
11
12
13 149 was that we focused on describing the prevalence of each disease and also assessing
14
15
16 150 the association of multimorbidity on hospitalisation or death. The CCI Canadian version
17
18
19 151 has been reported to be applicable to Japanese claims data.²¹ We therefore defined
20
21
22 152 diagnosed diseases using medical claims data following ICD-10 codes of the CCI
23
24
25 153 Canada version. We merged the conditions “diabetes with chronic complication” and
26
27
28 154 “diabetes without chronic complication” into “diabetes mellitus”, and “mild liver disease”
29
30
31 155 and “moderate or severe liver disease” into “liver disease”. The following 15 chronic
32
33
34 156 conditions were included: AIDS/HIV, any malignancy (including lymphoma and
35
36
37 157 leukaemia), cerebrovascular disease, chronic pulmonary disease, congestive heart
38
39
40 158 failure, dementia, diabetes mellitus, hemiplegia or paraplegia, metastatic solid tumour,
41
42
43 159 liver disease, myocardial infarction, peptic ulcer disease, renal disease, and
44
45
46 160 rheumatologic disease. The ICD-10 codes of these diseases are shown in eTable 1 in
47
48
49 161 the Supplement. Multimorbidity status was defined as the concurrent presence of two or
50
51
52 162 more (≥ 2) diagnosed diseases among these conditions.^{22, 23} We only used confirmed
53
54
55 163 diagnoses, not including suspected diagnoses, in Japanese claims data.
56
57
58
59
60

1
2
3
4 1645
6
7 165 *Definition of outcome events; hospitalisation or death*
8
9

10 166 We defined two composite outcomes, hospitalisation or death, which occurred during
11
12
13 167 the period from FY2015 to FY2018. Using the medical claims data, both events were
14
15
16 168 traced by month. In Japan, the validity of death event information is reported to be less
17
18
19 169 sensitive if derived from medical claims data only.^{24, 25} Therefore, we also used death
20
21
22 170 information from enrolment data recorded by the insurer: if either contained death
23
24
25 171 information, this was defined as a death event.

26
27
28 17229
30
31 173 *Estimation of diagnosed disease prevalence to a nationwide scale*
32
33

34 174 Diagnosed disease prevalence from baseline data was standardised to the
35
36
37 175 nationwide Japanese total population. We calculated prevalence rates according to
38
39
40 176 groups by 5-year age brackets and sex. Then, we estimated the prevalence rates
41
42
43 177 standardized to Japanese total population (age-sex standardized prevalence rate),
44
45
46 178 using the number from the vital statistics 2014 in Japan.²⁶

47
48
49 17950
51
52 180 *The association of multimorbidity with outcome by age group*
53
54
55
56
57
58
59
60

1
2
3
4 181 To examine the association of multimorbidity with outcome by age group, we
5
6
7 182 performed Cox regression analysis adjusted by sex using cohort data from four
8
9
10 183 consecutive years (FY2015 to FY2018). The independent and additive effect of
11
12
13 184 multimorbidity and aging, we defined combined categories according to three age
14
15
16 185 groups representing “young”, “middle”, and “old” ages (20-39, 40-59, and ≥ 60 ,
17
18
19 186 respectively) and the binary status of multimorbidity, with the reference set as no
20
21
22 187 multimorbidity individuals aged 20-39. This model was able to show HR for aging alone
23
24
25 188 (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity
26
27
28 189 and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-
29
30
31 190 39 ages without multimorbidity).

191

192 *Statistical analysis*

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

1
2
3
4 199 generation. Results were considered statistically significant at a two-sided P -value of
5
6
7 200 less than 0.05. All analyses were conducted using Stata software version 15.1
8
9
10 201 (StataCorp LLC; College Station, TX, USA).
11
12

13 202
14
15

16 203 *Patient and Public involvement*

17
18
19 204 Patients or the public were not involved in this research. However, the results of this
20
21
22 205 study will be disseminated to the public through various means including published
23
24
25 206 papers and presentations.
26

27 207
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

208 **Results**

209 *Study participants*

210 We analysed $n = 246\,671$ individuals in the baseline data set in FY2014 (Table1) and
211 $n = 181\,959$ individuals in the cohort data set FY2014-FY2018. Because the follow-up
212 was four years, the cohort data set was slightly smaller than the baseline data set,
213 especially as a number of young individuals aged 20-24 and older individuals aged >60
214 dropped out. This may be due to raising children or early retirement, and explains the
215 higher proportion of men in the cohort data set. Mean age and co-morbidity numbers
216 among CCI diseases were mostly comparable between the two data sets, although the
217 prevalence differed for diabetes mellitus, cerebrovascular disease, and chronic
218 pulmonary disease (eTable 2 in the Supplement). In the cohort data set, differences in
219 disease prevalence between genders were observed. Notably, men had a higher
220 prevalence of diabetes mellitus ($P = 0.001$) whereas women had a higher prevalence of
221 chronic pulmonary disease ($P = 0.002$).

222

223 *Estimated prevalence of multimorbidity in the Japanese total population*

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

1
2
3
4 226 estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population
5
6
7 227 (eTable 3A in the Supplement). The prevalence rate with age was increased , i.e.,
8
9
10 228 approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)),
11
12
13 229 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64
14
15
16 230 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of
17
18
19 231 diseases as well as the below results are shown in eTable 3B in the Supplement).
20
21
22 232 Figure 2B shows the types of diseases and their prevalence across age groups. The top
23
24
25 233 five diseases across the age groups “young” (20-39), “middle-aged (40-59), and “old”
26
27
28 234 (60-74) in order of prevalence were “young”: chronic pulmonary disease, peptic ulcer
29
30
31 235 disease, liver disease, diabetes mellitus, and any malignancy; “middle-aged”: chronic
32
33
34 236 pulmonary disease, diabetes mellitus, liver disease, peptic ulcer disease, and any
35
36
37 237 malignancy; and “old”: diabetes mellitus, chronic pulmonary disease, liver disease,
38
39
40 238 peptic ulcer disease, and cerebrovascular disease. Notably, diabetes mellitus moved up
41
42
43 239 across the age groups from ranking fourth to first. In Figure 2C, disease prevalence is
44
45
46 240 shown in comparison to disease prevalence in the 40-44 age group. After the age of 40-
47
48
49 241 44, the top five accelerating diseases were dementia, cerebrovascular disease,
50
51
52 242 peripheral vascular disease, metastatic tumour, and congestive heart failure.
53
54
55 243

1
2
3
4 244 The association of multimorbidity with outcome by age group.

5
6
7 245 The composite outcomes occurred 17.2% (death 0.8%, hospitalisation 16.9%) in the
8
9
10 246 follow-up period (eTable2). Cox regression analysis showed that young individuals aged
11
12
13 247 20-39 with multimorbidity had a higher hazard ratio (HR) compared to the same age
14
15
16 248 group without multimorbidity (HR = 2.43 [95% CI, 2.30-2.56]). Further, HRs increased
17
18
19 249 across age groups (HR = 2.55 [95% CI, 2.47-2.63] ages 40-59; HR = 3.41 [95% CI,
20
21
22 250 3.23-3.53] ages ≥ 60) (Fig. 3). The impact of multimorbidity on outcome exceeded that of
23
24
25 251 aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥ 60 and HR = 1.10 [95% CI, 1.07-1.13] ages
26
27
28 252 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with
29
30
31 253 multimorbidity has a risk more than ages ≥ 60 without multimorbidity.

32
33
34 254 We also assessed HRs for non-multimorbid and multimorbid women and men
35
36
37 255 separately and found that women had a lower HR than men in the 20-39 age group but
38
39
40 256 a higher HR than men in the ≥ 60 age group (eTable 4 in the Supplement).
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

258 Discussion

259 In this study we analysed nationwide medical claims data for 15 chronic diseases in a
260 large cohort of the general population of Japan. As key findings, standardised
261 prevalence rates for multimorbidity were estimated to 26.1% for men and 26.0% for
262 women. Further, age group-specific prevalence rates for multimorbidity ranged from
263 3.9% (20-24 years) to 14.6% (40-44 years) and 60.1% (70-74 years), showing an
264 accelerating increase after age 40. Importantly, significant differences in the clinical
265 outcomes of multimorbidity versus no multimorbidity were already present in young and
266 middle-aged individuals.

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

1
2
3
4 276 diseases associated with health-related quality of life loss. CCI originally includes
5
6
7 277 comorbidities that have a strong impact on mortality, not quality of life and well-being.
8
9
10 278 The presence of mental or psychosomatic disorders, which have been shown to be
11
12
13 279 increasing, particularly in individuals already suffering from other chronic diseases,²⁷
14
15
16 280 younger people,²⁸ and people with a low socio-economic status.²⁹ Such diseases often
17
18
19 281 remain undiagnosed or underreported in health records.³⁰ Also, we collected diseases
20
21
22 282 which were occurred during the year (FY2014). Therefore, patients who were untreated,
23
24
25 283 undiagnosed, or discontinued treatment cannot be picked up. These limitations likely
26
27
28 284 contributed to an underestimation of multimorbidity in our cohort. Further, because we
29
30
31 285 did not manually verify the presence of disease using the physician's medical records
32
33
34 286 data or medication information, disease names extracted from the medical claims data
35
36
37 287 might be incorrect in some cases. In particular, Japanese physicians sometimes change
38
39
40 288 the name of the disease in the medical record to the "correct" disease name for the
41
42
43 289 medication they wish to prescribe, a practice called "disease name for claims data".
44
45
46 290 Because of differences in data sources and study populations, direct comparison of
47
48
49 291 population-based prevalence rates between studies is not straightforward. Nonetheless,
50
51
52 292 the standardised prevalence rates for multimorbidity as reported in the present study -
53
54
55 293 26.1% for men and 26.0% for women - are similar to those reported by recent studies in

1
2
3
4 294 other high-income countries, such as the United States (25% in men, 25% in women),³¹
5
6
7 295 England (24.4% in men, 30% in women),³² Canada (24.3% whole population),⁵ and
8
9
10 296 Denmark (19.3% in men, 23.7% in women).⁶ Also recently some Asian countries
11
12
13 297 reported similar prevalence, Iran (13.4% in men, 25.0% in women),³³ India, and
14
15
16 298 Bangladesh (53.7% - 56.5% in both genders, over aged 60).³⁴ Many previous studies on
17
18
19 299 multimorbidity focused on the older generation, aged 65 and up, because of the larger
20
21
22 300 number of chronic diseases in this age group and the increasing number of people
23
24
25 301 entering it. However, our present data show that already approximately 10% of 30-34-,
26
27
28 302 19% of 45-49-, and 33% of 55-59-year-olds have ≥ 2 chronic diseases. Further, 1% of
29
30
31 303 30-34-, 4% of 45-49-, and 9% of 55-59-year-olds have ≥ 5 chronic diseases. These
32
33
34 304 results show that multimorbidity is already prominent in the middle-aged population.
35
36
37 305 Recent studies reported similar or slightly higher prevalence rates for ≥ 2 chronic
38
39
40 306 diseases in an American (8% of 30-, 20% of 45-, and 38% of 55-year-olds)²⁹ and a
41
42
43 307 Canadian (10.5% of 18-44-, 27.4% of 45-54-, and 46.6% of 55-64-year-olds)⁵
44
45
46 308 population, although these two studies also included mental diseases and osteoporosis,
47
48
49 309 which our present study did not. Our present study shows that, among 15 chronic
50
51
52 310 diseases, the top five diseases in the 55-64 age group are chronic pulmonary disease
53
54
55 311 (20.4-23.1%), diabetes mellitus (19.3-24.5%), liver disease (17.2-19.9%), peptic ulcer
56
57
58
59
60

1
2
3
4 312 disease (15.6-18.2%), and any malignancy (8.2-10.7%). With regard to diabetes
5
6
7 313 mellitus, the prevalence in the present study is similar to that previously reported in an
8
9
10 314 American population (15-30% in individuals aged 55-65)²⁹ but higher than that in a
11
12
13 315 Canadian population (16.6% in individuals aged 55-64)⁴. The prevalence of chronic
14
15
16 316 pulmonary disease in our present 55-65-year-olds was almost twice as high as those
17
18
19 317 seen for the combined prevalence of asthma and chronic obstructive pulmonary disease
20
21
22 318 (COPD) in an American population aged 55-65 years (5% for men and 10% for
23
24
25 319 women)²⁹ and in a Canadian population aged 55-64 years (13.7%).⁵ This difference
26
27
28 320 might have arisen due to our inclusion of various other pulmonary diseases besides
29
30
31 321 asthma and COPD. Regarding liver disease, the prevalence seen for 55-65-year-olds in
32
33
34 322 the present study was comparable to that seen in an adult population in Northern Italy³⁵
35
36
37 323 and in an adult population in Korea,³⁶ although this comparison requires care since the
38
39
40 324 types of liver disease in these studies and the age groups included vary.

41
42
43 325 Analysis of clinical outcomes using Cox regression revealed that the presence of
44
45
46 326 multimorbidity increased HRs in all age groups, including young individuals. In addition,
47
48
49 327 the comparison of the increased HRs resulting from multimorbidity versus no
50
51
52 328 multimorbidity showed that the impact of multimorbidity exceeds that of increasing age.
53
54
55 329 These results indicate that multimorbidity places a burden on all age groups.

1
2
3
4 330 The five most prevalent diseases (diabetes mellitus, chronic pulmonary disease, liver
5
6
7 331 disease, peptic ulcer disease, and any malignancy) in the present study are lifestyle-
8
9
10 332 related diseases that develop slowly over time. This trend should be greeted with alarm.
11
12
13 333 We trust that this study raises awareness of the potential health risks and burden
14
15
16 334 associated with the early onset of multimorbidity in young and middle-aged, the period
17
18
19 335 when one is busy working and raising children. Future studies should investigate the
20
21
22 336 specific lifestyle factors associated with an elevated risk of multimorbidity in the
23
24
25 337 Japanese working population. Ultimately, public health care policies should be aimed at
26
27
28 338 efforts to reverse the trend toward early multimorbidity onset.

31 339 In conclusion, the present study confirmed the prevalence of MM by including in the
32
33
34 340 denominator those who did not have the receipt of medical claims and to estimate the
35
36
37 341 prevalence of MM in the general population. Furthermore, we revealed that the impact
38
39
40 342 of multimorbidity is already clinically significant in middle-aged Japanese, with elevated
41
42
43 343 adverse events such as hospitalisation or death. In addition, the risk posed by
44
45
46 344 multimorbidity exceeds that of aging in all age groups. These results underscore the
47
48
49 345 need to undertake healthcare intervention against the onset of multimorbidity before
50
51
52 346 middle-aged, and not to leave it as a problem for geriatricians.

55 347
56
57
58
59
60

1
2
3
4 348 **Ethical Approval**

5
6
7 349 The present study was approved by the Institutional Review Board (IRB) of Kyoto
8
9
10 350 University (approval number: R0817). All data were anonymised before analysis and
11
12
13 351 none of the researchers had access to patient-identifiable information. The IRB waived
14
15
16 352 informed consent for this observational study.
17
18

19 353

20
21
22 354 **Data Availability Statement**

23
24
25 355 All data are incorporated into the article and its online supplementary material.
26
27

28 356

29
30
31 357 **Author Contributions**

32
33
34 358 Concept and design: YS, SF. Acquisition, analysis, or interpretation of data: all authors.
35
36

37 359 Drafting of the manuscript: YS, SF. Critical revision of the manuscript for important
38
39

40 360 intellectual content: all authors. Statistical analysis: YS, SF. Obtained funding: YS.
41
42

43 361 Administrative, technical, or material support: YS, SF. Study supervision: SF, AI, TN.
44
45

46 362 YS had full access to all the data in the study and takes responsibility for the integrity of
47
48

49 363 the data and the accuracy of the data analysis. All authors gave final approval and
50
51

52 364 agreed to be accountable for all aspects of work.
53
54

55 365
56
57
58
59
60

1
2
3
4 366 **Acknowledgements**
5

6
7 367 The authors are grateful to HIA²CE for providing data for the present study.
8
9

10 368

11
12
13 369 **Funding**
14

15
16 370 This work was supported by Grants-in-Aid from the Japan Society for the Promotion of
17
18
19 371 Science (JSPS) KAKENHI Grant Number 19K19458 (YS). The sponsor had no role in
20
21
22 372 the design of the study; in the collection, analysis and interpretation of data; in the
23
24
25 373 writing of the report; or in the decision to submit the article for publication.
26
27

28 374

29
30
31 375 **Competing Interests**
32

33
34 376 None declared.
35
36

37 377

38
39
40 378 **Patient Consent for Publication**
41

42
43 379 Not applicable.
44
45

46 380

47
48
49 381

50
51
52 382 **Figure Legends**
53

54
55 383 **Figure 1.** Participant selection flowchart. FY; fiscal year
56
57
58

1
2
3
4
5
6 384
7
8

9 385 **Figure 2.** Multimorbidity across age groups in the Japanese total population aged 20-
10 74. **A)** Percentage of the population having 0 to ≥ 5 chronic diseases by age group. **B)**
11
12 386
13
14
15 387 Prevalence of the top ten chronic diseases by age group. **C)** The top ten chronic
16
17
18 388 diseases with the steepest increase after age 40-44 years.
19

20
21 389
22
23

24 390 **Figure 3.** Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2
25
26
27 391 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese
28
29
30 392 aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval
31

32 393
33

394 **References**

- 34
35
36 395 1 Bleich SN, Sherrod C, Chiang A, *et al.* Systematic Review of Programs Treating
37
38 396 High-Need and High-Cost People With Multiple Chronic Diseases or Disabilities
39
40 397 in the United States, 2008-2014. *Prev Chronic Dis.* Nov 12 2015;12:E197.
41
42 398 doi:10.5888/pcd12.150275
43
44
45 399 2 Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative
46
47 400 review. *Prev Med Rep.* Dec 2018;12:284-293. doi:10.1016/j.pmedr.2018.10.008
48
49
50 401 3 Prathapan S, Fernando G, Matthias AT, Bentota Mallawa Arachchige Charuni Y,
51
52 402 Abeygunawardhana HMG, Somathilake B. The rising complexity and burden of
53
54
55
56
57
58
59
60

- 1
2
3 403 multimorbidity in a middle-income country. *PLoS One*. 2020;15(12):e0243614.
4
5 404 doi:10.1371/journal.pone.0243614
6
7
8 405 4 Low LL, Kwan YH, Ko MSM, *et al*. Epidemiologic Characteristics of Multimorbidity
9
10 406 and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging
11
12 407 Asian Country. *JAMA Netw Open*. Nov 1 2019;2(11):e1915245.
13
14 408 doi:10.1001/jamanetworkopen.2019.15245
15
16
17 409 5 Pefoyo AJ, Bronskill SE, Gruneir A, *et al*. The increasing burden and complexity of
18
19 410 multimorbidity. *BMC Public Health*. Apr 23 2015;15:415. doi:10.1186/s12889-015-
20
21 411 1733-2
22
23
24 412 6 Schiotz ML, Stockmarr A, Host D, Glumer C, Frolich A. Social disparities in the
25
26 413 prevalence of multimorbidity - A register-based population study. *BMC Public*
27
28 414 *Health*. May 10 2017;17(1):422. doi:10.1186/s12889-017-4314-8
29
30
31 415 7 Sum G, Ishida M, Koh GC, Singh A, Oldenburg B, Lee JT. Implications of
32
33 416 multimorbidity on healthcare utilisation and work productivity by socioeconomic
34
35 417 groups: Cross-sectional analyses of Australia and Japan. *PLoS One*.
36
37 418 2020;15(4):e0232281. doi:10.1371/journal.pone.0232281
38
39
40 419 8 Bahler C, Huber CA, Brungger B, Reich O. Multimorbidity, health care utilization
41
42 420 and costs in an elderly community-dwelling population: a claims data based
43
44 421 observational study. *BMC Health Serv Res*. Jan 22 2015;15:23.
45
46 422 doi:10.1186/s12913-015-0698-2
47
48
49 423 9 Hu RH, Hsiao FY, Chen LJ, Huang PT, Hsu WW. Increasing age- and gender-
50
51 424 specific burden and complexity of multimorbidity in Taiwan, 2003-2013: a cross-
52
53
54
55
56
57
58
59
60

- 1
2
3 425 sectional study based on nationwide claims data. *BMJ Open*. Jun 9
4
5 426 2019;9(6):e028333. doi:10.1136/bmjopen-2018-028333
6
7
8 427 10 Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in
9
10 428 relation to age, gender and immigrant status: a cross-sectional study based on
11
12 429 administrative data. *BMJ Open*. Dec 21 2016;6(12):e012812.
13
14 430 doi:10.1136/bmjopen-2016-012812
15
16
17 431 11 Picco L, Achilla E, Abdin E, *et al*. Economic burden of multimorbidity among older
18
19 432 adults: impact on healthcare and societal costs. *BMC Health Serv Res*. May 10
20
21 433 2016;16:173. doi:10.1186/s12913-016-1421-7
22
23
24 434 12 van den Bussche H, Schon G, Kolonko T, *et al*. Patterns of ambulatory medical
25
26 435 care utilization in elderly patients with special reference to chronic diseases and
27
28 436 multimorbidity--results from a claims data based observational study in Germany.
29
30 437 *BMC Geriatr*. Sep 13 2011;11:54. doi:10.1186/1471-2318-11-54
31
32
33 438 13 Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of
34
35 439 risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a
36
37 440 longitudinal analysis of the Twenty-07 cohort. *BMC Med*. Aug 24 2017;15(1):152.
38
39 441 doi:10.1186/s12916-017-0913-6
40
41
42 442 14 Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising
43
44 443 burden of multimorbidity and related socio-demographic factors: a repeated
45
46 444 cross-sectional study of Ontarians. *Can J Public Health*. Apr 13
47
48 445 2021;doi:10.17269/s41997-021-00474-y
49
50
51 446 15 Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in
52
53 447 multimorbidity, complex multimorbidity and multiple functional limitations in the
54
55
56
57
58
59
60

- 1
2
3 448 ageing population of England, 2002-2015. *J Comorb.* Jan-Dec
4
5 449 2019;9:2235042X19872030. doi:10.1177/2235042X19872030
6
7
8 450 16 Katsutoshi H, Annabel B, Yasuhiko M, et al. Current Status, Challenges, and
9
10 451 Future Perspectives of Real-World Data and Real-World Evidence in Japan.
11
12 452 *Drugs - Real World Outcomes.* 2021;8:459–480. doi:org/10.1007/s40801-021-
13
14 453 00266-3
15
16
17 454 17 Eng SL, Hui LK, Elaine QY H, Sok HT, et al. Systematic review on the instruments
18
19 455 used for measuring the association of the level of multimorbidity and clinically
20
21 456 important outcomes. *BMJ Open.* 2021;May
22
23 457 5;11(5):e041219. doi:10.1136/bmjopen-2020-041219.
24
25
26 458 18 Karen B, Stewart WM, Michael N, et al. Epidemiology of multimorbidity and
27
28 459 implications for health care, research, and medical education: a cross-sectional
29
30 460 study. *Lancet.* 2012;Jul 7;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2.
31
32
33 461 19 Jürisson M, Heti P, Anneli U, et al. Prevalence of chronic conditions and
34
35 462 multimorbidity in Estonia: a population-based cross-sectional study. *BMJ Open.*
36
37 463 2021;Oct 5;11(10):e049045. doi:10.1136/bmjopen-2021-049045.
38
39
40 464 20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying
41
42 465 prognostic comorbidity in longitudinal studies: development and validation. *J*
43
44 466 *Chronic Dis.* 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-821 Quan
45
46 467 H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index
47
48 468 and score for risk adjustment in hospital discharge abstracts using data from 6
49
50 469 countries. *Am J Epidemiol.* Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433
51
52
53
54
55
56
57
58
59
60

- 1
2
3 470 21 Vijaya S, Hude Q, Patricia H, Kiyohide F. Cross-National Comparative
4
5 Performance of Three Versions of the ICD-10 Charlson Index. *Medical Care*.
6 471
7
8 472 2007 Dec;45(12):1210-5. doi: 10.1097/MLR.0b013e3181484347.
9
- 10 473 22 Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring
11
12 474 multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*.
13
14 475 Feb 1 2019;29(1):182-189. doi:10.1093/eurpub/cky098
16
- 17 476 23 Le Reste JY, Nabbe P, Manceau B, *et al*. The European General Practice
18
19 477 Research Network presents a comprehensive definition of multimorbidity in family
20
21 478 medicine and long term care, following a systematic review of relevant literature.
22
23 479 *J Am Med Dir Assoc*. May 2013;14(5):319-25. doi:10.1016/j.jamda.2013.01.001
25
- 26 480 24 Ooba N, Setoguchi S, Ando T, *et al*. Claims-based definition of death in Japanese
27
28 481 claims database: validity and implications. *PLoS One*. 2013;8(5):e66116.
29
30 482 doi:10.1371/journal.pone.0066116
32
- 33 483 25 Sakai M, Ohtera S, Iwao T, *et al*. Validation of claims data to identify death among
34
35 484 aged persons utilizing enrollment data from health insurance unions. *Environ*
36
37 485 *Health Prev Med*. Nov 23 2019;24(1):63. doi:10.1186/s12199-019-0819-3
39
- 40 486 26 Statistics Bureau of Japan. Preliminary count of the Japanese population.
41
42 487 Accessed March, 2014. <http://www.stat.go.jp/data/jinsui/index.html>
44
- 45 488 27 Aoki T, Yamamoto Y, Shimizu S, Fukuhara S. Physical multimorbidity patterns and
46
47 489 depressive symptoms: a nationwide cross-sectional study in Japan. *Fam Med*
48
49 490 *Community Health*. 2020;8(1):e000234. doi:10.1136/fmch-2019-000234
50
- 51 491 28 Egede LE. Major depression in individuals with chronic medical disorders:
52
53 492 prevalence, correlates and association with health resource utilization, lost
54
55
56
57
58
59
60

- 1
2
3 493 productivity and functional disability. *Gen Hosp Psychiatry*. Sep-Oct
4
5 494 2007;29(5):409-16. doi:10.1016/j.genhosppsych.2007.06.002
6
7
8 495 29 Rocca WA, Boyd CM, Grossardt BR, *et al*. Prevalence of multimorbidity in a
9
10 496 geographically defined American population: patterns by age, sex, and
11
12 497 race/ethnicity. *Mayo Clin Proc*. Oct 2014;89(10):1336-49.
13
14 498 doi:10.1016/j.mayocp.2014.07.010
15
16
17 499 30 Cassell A, Edwards D, Harshfield A, *et al*. The epidemiology of multimorbidity in
18
19 500 primary care: a retrospective cohort study. *Br J Gen Pract*. Apr
20
21 501 2018;68(669):e245-e251. doi:10.3399/bjgp18X695465
22
23
24 502 31 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al*. Comparison of the
25
26 503 information provided by electronic health records data and a population health
27
28 504 survey to estimate prevalence of selected health conditions and multimorbidity.
29
30
31 505 *BMC Public Health*. Mar 21 2013;13:251. doi:10.1186/1471-2458-13-251
32
33 506 32 St Sauver JL, Boyd CM, Grossardt BR, *et al*. Risk of developing multimorbidity
34
35 507 across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ*
36
37 508 *Open*. Feb 3 2015;5(2):e006413. doi:10.1136/bmjopen-2014-006413
38
39
40 509 33 Masoomah A, Azam M, Mehdi Y. *et al*. Multimorbidity as an important issue among
41
42 510 women: results of a gender difference investigation in a large population-based
43
44 511 cross-sectional study in West Asia. *BMJ Open*. 2017;May 9;7(5):e013548. doi:
45
46 512 10.1136/bmjopen-2016-013548.
47
48
49 513 34 Sanghamitra P, Subhashisa S, Mohammad AH, *et al*. Prevalence and outcomes of
50
51 514 multimorbidity in South Asia: a systematic review *bmj open*. *BMJ Open*. 2015 Oct
52
53 515 7;5(10):e007235. doi:10.1136/bmjopen-2014-007235.
54
55
56
57
58
59
60

1
2
3 516 35 Bellentani S, Tiribelli C, Saccoccio G, *et al.* Prevalence of chronic liver disease in
4
5 the general population of northern Italy: the Dionysos Study. *Hepatology*. Dec
6 517
7 1994;20(6):1442-9. doi:10.1002/hep.1840200611
8 518
9

10 519 36 Park SH, Plank LD, Suk KT, *et al.* Trends in the prevalence of chronic liver
11
12 disease in the Korean adult population, 1998-2017. *Clin Mol Hepatol*. Apr
13 520
14 2020;26(2):209-215. doi:10.3350/cmh.2019.0065
15 521
16

17 522

18
19 523
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 524 **Supplementary Information**
4

5
6 525

7
8 526 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define

9
10 527 diseases in medical claims data

11
12 528 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and

13
14 529 cohort data

15
16
17 530 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied

18
19 531 to the Japanese total population by gender

20
21 532 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied

22
23 533 to the Japanese total population by age group

24
25
26 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on

27
28 hospitalisation or death rates in a 5-year cohort of $n = 111\,088$ men and

29
30
31 $n = 70\,871$ women. Cox regression analysis

32
33 534
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

535 **Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese**
 536 **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

537

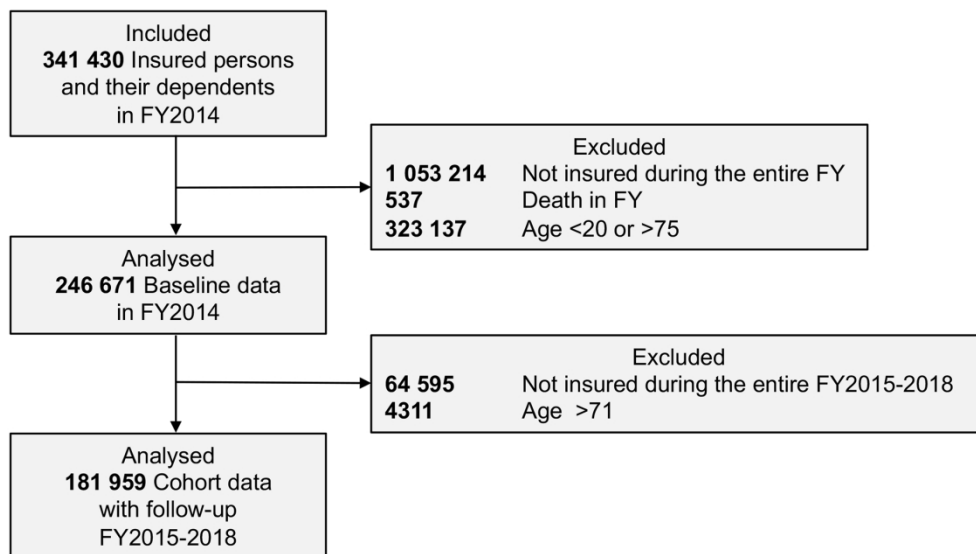


Figure 1. Participant selection flowchart. FY; fiscal year

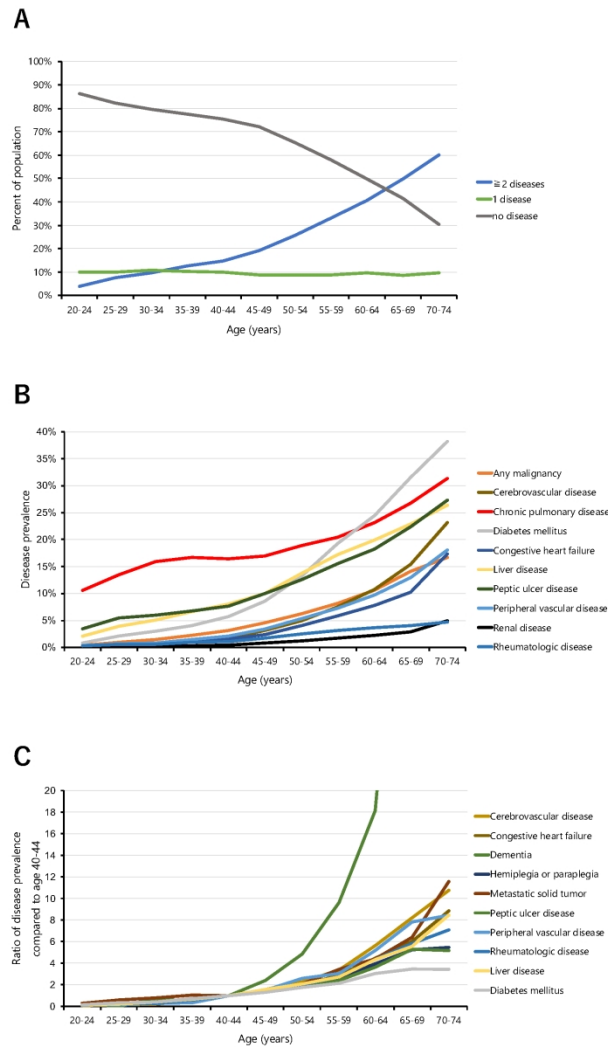


Figure 2. Multimorbidity across age groups in the Japanese total population aged 20-74. A) Percentage of the population having 0 to ≥ 5 chronic diseases by age group. B) Prevalence of the top ten chronic diseases by age group. C) The top ten chronic diseases with the steepest increase after age 40-44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

297x420mm (200 x 200 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

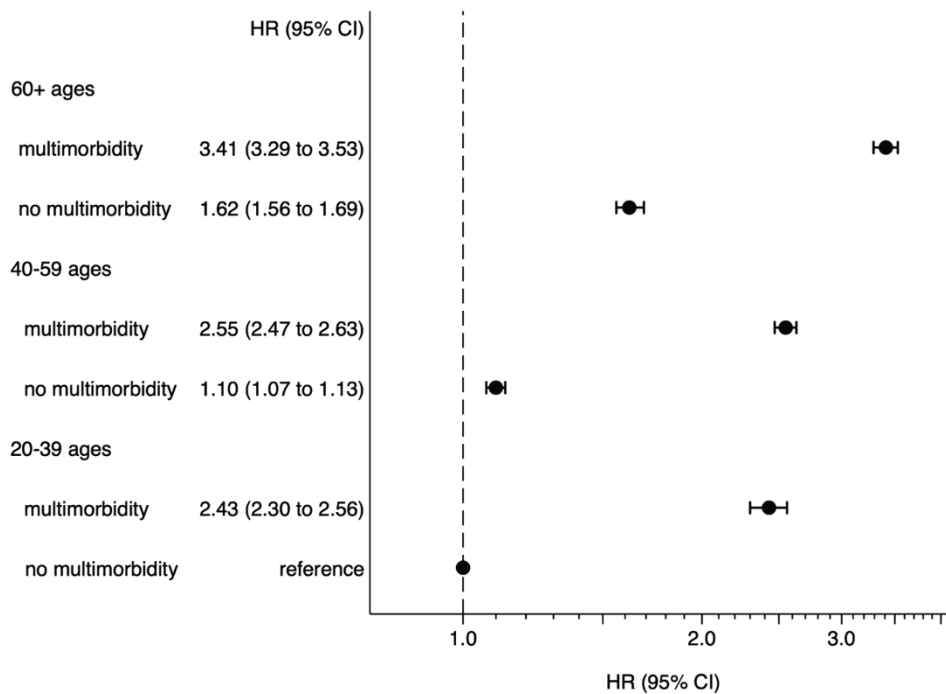


Figure 3. Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity (≥ 2 diagnosed diseases) in three age groups in a 5-year cohort of $n = 181\ 959$ Japanese aged 20-71. Cox regression analysis. HR; hazard ratio, CI; confidence interval

1
2
3 Supplementary material
4
5

6 Title: The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a
7 retrospective cohort study using nationwide medical claims data in the middle-aged generation
8
9

10
11 Authors: Yoshiyuki Saito PharmD, Ataru Igarashi PhD, Takeo Nakayama MD PhD, Shingo Fukuma MD
12
13

14
15
16 **Supplementary eTable 1.** List of diseases and their ICD-10 codes used to define diseases in medical claims data
17

18 **Supplementary eTable 2.** Characteristics of baseline data in fiscal year 2014 and cohort data
19

20 **Supplementary eTable 3A.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
21 by gender
22

23 **Supplementary eTable 3B.** Diagnosed disease prevalence in fiscal year 2014 applied to the Japanese total population
24 by age group
25
26

27 **Supplementary eTable 4.** Hazard ratios in multimorbid individuals based on hospitalisation or death rates in a 5-year
28 cohort of $n = 111\,088$ men and $n = 70\,871$ women. Cox regression analysis
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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-C41.x, 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
<i>N</i>	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 Disease no. among CCI	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
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)

1 Values are numbers (%) unless otherwise

2 ^aAny malignancy includes leukemia and
3 lymphoma.

4 FY; fiscal year

5 SD; standard deviation

6 CCI; Charlson Comorbidity Index

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

For peer review only

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%)

^aAny 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%)

^aAny 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%)
---	------------	---------	-----------	---------	-----------	---------	-----------	---------

^aAny 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%)

^aAny 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

^aReferences are female for sex, no disease for morbidity variables

^bReference 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 (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 (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Suppl. Table 2 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 (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	16, Fig. 3
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.