

Occupational Class and Risk of Cardiovascular Disease Incidence in Japan: Nationwide, Multicenter, Hospital-Based Case-Control Study

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Background—In contemporary Western settings, higher occupational class is associated with lower risk for cardiovascular disease (CVD) incidence, including coronary heart disease (CHD) and stroke. However, in non-Western settings (including Japan), the occupational class gradient for cardiovascular disease risk has not been characterized.

Methods and Results—Using a nationwide, multicenter hospital inpatient data set (1984–2016) in Japan, we conducted a matched hospital case-control study with ≈ 1.1 million study subjects. Based on a standard national classification, we coded patients according to their longest-held occupational class (blue-collar, service, professional, manager) within each industrial sector (blue-collar, service, white-collar). Using blue-collar workers in blue-collar industries as the referent group, odds ratios and 95% CIs were estimated by conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital. Smoking and drinking were additionally controlled. Higher occupational class (professionals and managers) was associated with excess risk for CHD. Even after controlling for smoking and drinking, the excess odds across all industries remained significantly associated with CHD, being most pronounced among managers employed in service industries (odds ratio, 1.19; 95% CI, 1.08–1.31). On the other hand, the excess CHD risk in higher occupational class was offset by their lower risk for stroke (eg, odds ratio for professionals in blue-collar industries, 0.77; 95% CI, 0.70–0.85).

Conclusions—The occupational “gradient” in cardiovascular disease (with lower risk observed in higher status occupations) may not be a universal phenomenon. In contemporary Japanese society, managers and professionals may experience higher risk for CHD. (*J Am Heart Assoc.* 2019;8:e011350. DOI: 10.1161/JAHA.118.011350.)

Key Words: cardiovascular disease • case-control study • cerebrovascular disease • Japan • occupational class • risk factor • socioeconomic gradient

In developed countries, cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, accounts for a high burden of morbidity and mortality.¹ Although CVD mortality has been declining in the United States as well as in Japan, it accounted for 32% of deaths in 2010 in the United States and is the second leading cause of death in Japan (after cancer).^{2,3}

Occupational class is considered to be a fundamental social determinant for CVD risk.² In Western settings, including Europe, United States, and Australia, an excess risk

of CVD among lower occupational class workers (blue-collar and service workers) is consistently reported.^{4–8} The occupational class “gradient” in CVD is in turn attributed to unequal exposures to adverse working conditions (eg, job strain, job insecurity, shift work, sedentarism, secondhand smoke exposure).^{7,9–12} Exposure to psychosocial work stress is hypothesized to directly increase CVD risk (eg, through allostatic load and inflammation), as well as indirectly through the patterning of risk behaviors, such as cigarette smoking, excessive drinking, poor sleep, and poor nutrition.^{7,8,13,14}

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Clinical Perspective

What Is New?

- In Western countries, the risk of cardiovascular disease is consistently higher in lower status occupations (eg, unskilled workers) compared with higher status occupations (eg, professionals).
- However, in contemporary Japanese society, the pattern of risk was observed to be in the opposite direction, namely, workers in higher status occupations (managerial and professional positions) experienced higher risk for coronary heart disease.
- We found opposite directions of socioeconomic gradients for coronary heart disease and stroke, suggesting that excess risk of coronary heart disease among managers and professionals may be offset by their reduced risk of stroke.

What Are the Clinical Implications?

- The inverse socioeconomic gradient in cardiovascular disease (with lower risk observed in higher status occupations) may not be a universal phenomenon.
- Accordingly, clinicians should adapt their advice to patients based on local realities.
- For example, encouraging the cessation of smoking is a priority for professional/managerial workers in Japan.

However, the “typical” occupational class gradient in CVD that we have come to expect in contemporary Western settings has not been universally observed across time and space.¹⁵ For example, in Japan, while high-quality medical care has been achieved irrespective of socioeconomic status through universal health coverage, annual health check-ups, and community-based comprehensive emergency medical service networks,^{16–20} the socioeconomic distribution of major risk behaviors differs markedly from Western countries. Specifically, we have observed that higher-occupational class individuals tend to smoke and drink as much (or sometimes even more) compared with their lower-occupational class counterparts.^{21,22} The reason for this pattern is thought to be related to the high levels of job stress among managerial occupations in Japan, stemming from long hours of (unpaid) overtime work as well as the hierarchical corporate structure in Japanese companies and the highly emphasized concept of hospitality to meet customers’ expectations.²³ Another potential reason would be the lax social norms on smoking and drinking, eg, as evidenced by the lack of national legislation to restrict indoor smoking.²³

Accordingly, the goal of the present study was to examine the association between the longest-held occupational class, a proxy for life-long socioeconomic status (SES), and risk for CVD incidence in Japan. Using a nationwide, multicenter inpatient database that includes

details of individual-level occupational and clinical information, we sought to describe the occupational class gradient in CHD incidence in Japan.

Methods

Study Setting

The data that support the findings of this study are available from the Japan Organization of Occupational Health and Safety, but restrictions apply to the availability of these data; they were used under the research agreement for the current study and so are not publicly available. If any person wishes to verify our data, they are most welcome to contact the corresponding author. Using the nationwide clinical and occupational data set (1984–2016) from the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), administered by Japan Organization of Occupational Health and Safety, a multicenter, hospital-based matched case-control study was conducted. Details of ICOD-R and the design of the study have been described elsewhere.^{23–27} Briefly, the Rosai Hospital group consists of 33 general hospitals in Japan; it has collected medical chart information confirmed by physicians (including basic sociodemographic characteristics, clinical history and diagnosis of current and

Table 1. The Number of Each Circulatory Disease Sites Among Patients Aged 20 Years and Older in the Nationwide Inpatient Data Set (1984–2016) From the Inpatient Clinico-Occupational Database of Rosai Hospital Group in Japan

Sites	ICD-9	ICD-10	n (%)
All sites	390–459	I00–99	128 615 (100)
Ischemic heart disease	410–414	I20–25	30 948 (24.1)
Coronary heart disease	413, 410	I20, 21	27 452 (21.3)
Angina pectoris	413	I20	19 781 (15.4)
Acute myocardial infarction	410	I21	7671 (6.0)
Cerebrovascular disease	430–438	I60–69	51 507 (40.0)
Stroke	430–432, 434	I60–63	41 038 (31.9)
Subarachnoid hemorrhage	430	I60	4704 (3.7)
Intracerebral hemorrhage	431	I61	10 245 (8.0)
Cerebral infarction	434	I63	22 242 (17.3)

ICD-9 indicates *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*.

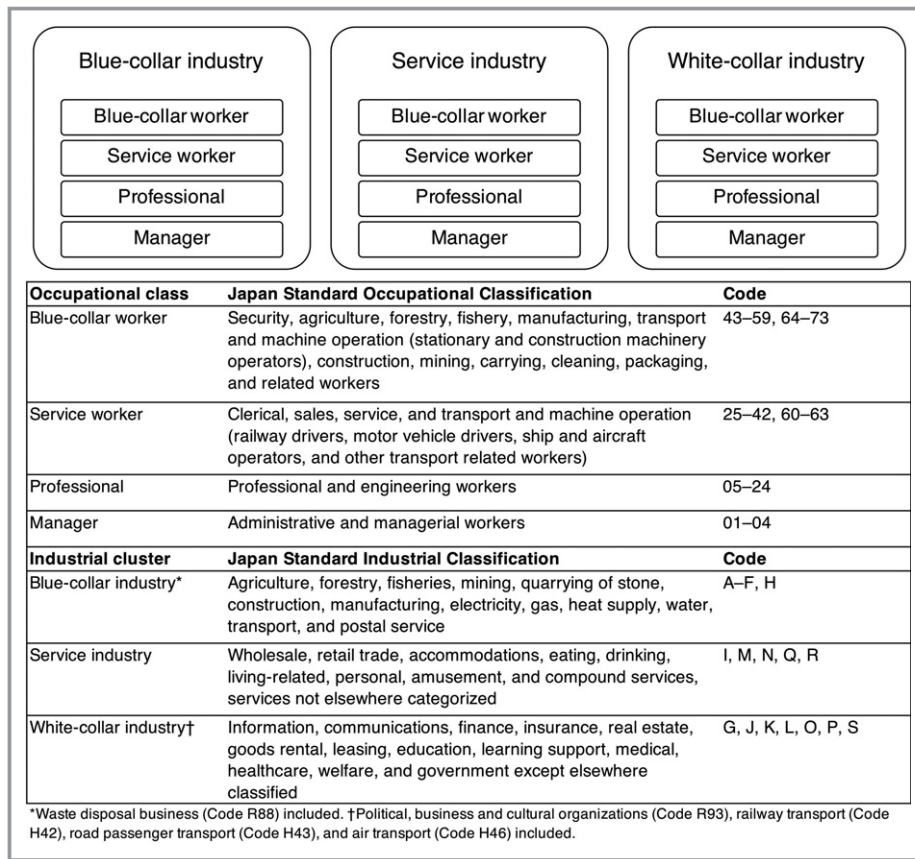


Figure 1. Longest-held occupational class, cross-classified with industrial sector.

past diseases, treatment, and outcome for every inpatient) since 1984.^{23–27} The clinical diagnosis and comorbid diseases extracted from physicians' medical charts confirmed at discharge are coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)* or *Tenth Revision (ICD-10)*.^{23–27} The major profile of backgrounds (including sex, age,

and occupational class) among patients in the ICD-R data parallels the Japanese national data.^{23,24,27}

From questionnaires completed at the time of admission, the database includes the occupational history of each inpatient (current and 3 most recent jobs, including the age of starting and ending) as well as smoking and alcohol habits.^{23–27} The detailed occupational history is coded using the standardized 3-digit codes of the Japan Standard Occupational Classification and Japan Standard Industrial Classification. These correspond, respectively, to the International Standard Occupational Classification and International Standard Occupational Classification; Japan Organization of Occupational Health and Safety updated the previous job codes to be consistent with changes in coding practice according to the revisions of the standardized national classification.^{23–27} Written informed consent was obtained before patients completed the questionnaires; trained registrars and nurses are responsible for registering the data. The database currently contains details from >6 million inpatients.

We obtained a deidentified data set under the research agreement between the authors and Japan Organization of Occupational Health and Safety. The research ethics committees of The University of Tokyo, Tokyo (Protocol Number

Table 2. Difference Between Those With Complete Data and Those With Incomplete Data

Characteristics*	n (%) or Mean (SD)		P Value
	Incomplete (n=68 181)	Complete (n=1 060 410)	
Case	25 210 (37%)	103 405 (9.8%)	<0.001
Sex, female	4923 (7.2%)	228 412 (22%)	<0.001
Age, y	45 (15)	61 (12)	<0.001
Admission date, financial (y)	1998 (9)	2001 (8)	<0.001

P values for t test or Chi-squared test.

*The distribution of admitting hospitals differed between those with complete data and those with incomplete data ($P<0.001$).

Table 3. Background Characteristics Between Cases and Controls

Characteristics*	n (%) or Mean (SD)		P Value†
	Control (n=999 976)	Case (n=128 615)	
Female	202 743 (20.3%)	30 592 (23.8%)	<0.001
Age, y	60 (13)	61 (14)	<0.001
Admission date, financial (y)	2001 (8)	2001 (9)	0.13
Occupational class‡	n=957 005	n=103 405	<0.001
Blue-collar industry			
Blue-collar	347 239 (36.3%)	38 824 (37.5%)	
Service	123 213 (12.9%)	12 533 (12.1%)	
Professional	33 755 (3.5%)	2987 (2.9%)	
Manager	38 611 (4.0%)	3960 (3.8%)	
Service industry			
Blue-collar	38 609 (4.0%)	4403 (4.3%)	
Service	156 424 (16.3%)	18 724 (18.1%)	
Professional	8399 (0.9%)	881 (0.9%)	
Manager	19 189 (2.0%)	2055 (2.0%)	
White-collar industry			
Blue-collar	19 711 (2.1%)	1985 (1.9%)	
Service	88 800 (9.3%)	8661 (8.4%)	
Professional	69 905 (7.3%)	7179 (6.9%)	
Manager	13 150 (1.4%)	1213 (1.2%)	
Log-transformed pack-year‡	n=919 976	n=101 458	0.32
	1.90 (1.79)	1.90 (1.79)	
Log-transformed daily ethanol intake‡	n=826 329	n=92 297	<0.001
	2.07 (1.77)	1.95 (1.82)	

*Distribution of admitting hospitals statistically differed between the cases and controls ($P<0.001$).

†P-values were for *t* test and Chi-squared test.

‡Variables contained missing data. Percentage may not total 100 because of rounding.

3890-5) and Kanto Rosai Hospital, Kanagawa (Protocol Number 2014-38) approved the study.

Cases and Controls

The study subjects comprised 1 128 591 patients (128 615 CVD cases and 999 976 controls), aged ≥ 20 years admitted to the hospital between 1984 and 2016. To select cases and controls from the same population, we randomly sampled 10 controls for each case, matched by sex (men/women), age (in the same 5-year age category), admission date (in the same financial year), and admitting hospital (in the same admitting hospital).^{24,26,27} The matching process, however, generated fewer than 10 controls for some cases (the average number of controls for each case, 8 [range 1–10];

the percentage of cases matched to 10 controls, 54.9%). The mean age [mean (SD)] for the original population and the matched population was, respectively, 55 (19) years and 60 (13) years. Controls who were later hospitalized for CVD were not eligible to be cases.

The cases were those patients whose main diagnosis was initial CVD (*ICD-9*, 390–459 and *ICD-10*, I00–I99), confirmed by physicians at discharge along with clinical examinations or treatments, including ECGs, computerized tomography scans, catheter angiography/intervention, and surgery. We defined CVD incidence as the first ever hospital admission among patients who did not have a previous history of any CVDs. Validation for the diagnosis corresponding to *ICD-9* or *ICD-10* in the database has been described elsewhere.^{23–27} The database is unique to the Rosai Hospital group, therefore it differs from medical claims data, which may be less accurate for diagnosis.²⁸ We specified CHD, which comprised with angina pectoris (*ICD-9*, 413 and *ICD-10*, I20) and acute myocardial infarction (*ICD-9*, 410 and *ICD-10*, I21, Table 1). We also specified stroke, which comprised with subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction (Table 1).

Based on the methodology used in previous studies, our controls comprised patients admitted to the hospitals with the following diagnoses, which were not related to occupational class in ICOD-R^{23,24,27}: eye and ear disease (*ICD-9*, 360–389 and *ICD-10*, H00–H95; 31.1%), genitourinary disease (*ICD-9*, 580–629 and *ICD-10*, N00–N99; 31.1%), infection (*ICD-9*, 1–136 and *ICD-10*, A00–B99; 10.7%), skin diseases (*ICD-9*, 680–709 and *ICD-10*, L00–L99; 5.9%), symptoms and ill-health conditions (*ICD-9*, 780–799 and *ICD-10*, R00–R99; 7.3%), or other diseases such as congenital malformations (*ICD-9*, 280–289, 740–779, and *ICD-10*, D50–D77, P00–P96, Q00–Q99; 13.9%). We excluded controls (1) who had a history of CVD or (2) who were not admitted to the hospitals for the first time.

Longest-Held Occupational Class Cross-Classified by Industry Sector

To classify occupational class from the comprehensive list of occupations (current and up to 3 most recent jobs) listed in ICOD-R, we grouped the longest-held occupation for each patient into 1 of 4 occupational classes: blue-collar, service, professional, and manager. Each patient was also cross-classified into 1 of 3 industrial sectors: blue-collar, service, and white-collar, based on the approach adopted in previous studies (Figure 1).^{23,24,27} Those who were not actively engaged in paid employment, such as homemakers, students, and unemployed workers, were excluded. The average length of the longest held jobs was 27 years in ICOD-R, and the length was not significantly associated with risk for CVD in a

Table 4. Odds Ratios of Each Occupational Class Associated With Risk for Coronary Heart Disease, Stroke, and Overall CVD Incidence

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1 [†]	P Value	Model 2 [‡]	P Value
Coronary heart disease	n=226 378	n=27 452				
Occupational class						
Blue-collar industry						
Blue-collar	34.6	33.6	1.00		1.00	
Service	13.9	13.8	1.09 (1.04–1.13)	<0.001	1.08 (1.04–1.13)	<0.001
Professional	4.1	3.8	1.05 (0.97–1.13)	0.22	1.07 (0.99–1.16)	0.08
Manager	4.5	4.9	1.19 (1.11–1.27)	<0.001	1.19 (1.11–1.27)	<0.001
Service industry						
Blue-collar	4.1	3.9	1.01 (0.94–1.09)	0.83	1.01 (0.93–1.08)	0.86
Service	15.8	16.8	1.10 (1.06–1.15)	<0.001	1.10 (1.06–1.15)	<0.001
Professional	0.9	0.9	1.13 (0.97–1.32)	0.11	1.16 (0.99–1.35)	0.06
Manager	2.2	2.4	1.20 (1.09–1.31)	<0.001	1.19 (1.08–1.31)	<0.001
White-collar industry						
Blue-collar	2.1	2.1	1.07 (0.98–1.18)	0.15	1.08 (0.99–1.19)	0.09
Service	9.4	9.2	1.04 (0.99–1.09)	0.17	1.05 (1.00–1.11)	0.05
Professional	7.0	7.0	1.05 (0.99–1.11)	0.08	1.10 (1.04–1.17)	<0.001
Manager	1.5	1.5	1.06 (0.94–1.19)	0.35	1.06 (0.95–1.19)	0.29
Log-transformed pack-year, mean	2.1	2.3			1.15 (1.14–1.16)	<0.001
Log-transformed daily ethanol intake, mean	2.3	2.2			0.95 (0.94–0.96)	<0.001
Angina pectoris	n=163 736	n=19 781				
Occupational class						
Blue-collar industry						
Blue-collar	34.1	32.8	1.00		1.00	
Service	13.9	14.1	1.12 (1.06–1.18)	<0.001	1.11 (1.05–1.17)	<0.001
Professional	4.1	4.0	1.10 (1.00–1.21)	0.04	1.11 (1.02–1.22)	0.02
Manager	4.4	4.9	1.24 (1.14–1.34)	<0.001	1.23 (1.14–1.33)	<0.001
Service industry						
Blue-collar	4.1	3.7	0.92 (0.84–1.01)	0.08	0.92 (0.84–1.01)	0.07
Service	16.2	16.9	1.08 (1.03–1.14)	<0.001	1.08 (1.03–1.13)	0.001
Professional	0.9	0.9	1.13 (0.90–1.42)	0.27	1.15 (0.92–1.45)	0.20
Manager	2.2	2.4	1.21 (1.08–1.35)	0.001	1.19 (1.07–1.34)	0.002
White-collar industry						
Blue-collar	2.1	2.1	1.11 (0.99–1.24)	0.07	1.12 (1.00–1.25)	0.05
Service	9.4	9.3	1.05 (0.99–1.11)	0.11	1.06 (1.00–1.12)	0.05
Professional	7.1	7.4	1.08 (1.01–1.15)	0.02	1.12 (1.05–1.19)	<0.001
Manager	1.5	1.5	1.12 (0.98–1.28)	0.09	1.12 (0.98–1.28)	0.08
Log-transformed pack-year, mean	2.0	2.2			1.11 (1.10–1.12)	<0.001
Log-transformed daily ethanol intake, mean	2.2	2.2			0.98 (0.97–0.99)	<0.001
Acute myocardial infarction	n=62 642	n=7671				

Continued

Table 4. Continued

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1 [†]	P Value	Model 2 [‡]	P Value
Occupational class						
Blue-collar industry						
Blue-collar	35.8	35.6	1.00		1.00	
Service	13.9	13.0	1.01 (0.93–1.11)	0.79	1.01 (0.92–1.10)	0.85
Professional	4.1	3.5	0.92 (0.80–1.06)	0.26	0.97 (0.85–1.12)	0.70
Manager	4.7	4.8	1.07 (0.95–1.21)	0.28	1.07 (0.95–1.22)	0.26
Service industry						
Blue-collar	3.9	4.7	1.25 (1.09–1.42)	0.002	1.25 (1.09–1.43)	0.001
Service	14.6	16.3	1.16 (1.07–1.26)	<0.001	1.16 (1.07–1.26)	<0.001
Professional	0.9	0.9	1.12 (0.82–1.52)	0.47	1.17 (0.86–1.59)	0.32
Manager	2.2	2.5	1.18 (1.00–1.38)	0.05	1.18 (1.00–1.39)	0.05
White-collar industry						
Blue-collar	2.3	2.2	0.98 (0.78–1.24)	0.89	1.00 (0.78–1.28)	>0.99
Service	9.4	8.9	1.01 (0.91–1.11)	0.91	1.03 (0.93–1.14)	0.53
Professional	6.6	6.2	0.98 (0.85–1.12)	0.73	1.06 (0.92–1.23)	0.37
Manager	1.5	1.3	0.90 (0.67–1.21)	0.46	0.92 (0.68–1.24)	0.57
Log-transformed pack-year, mean	2.2	2.6			1.25 (1.22–1.27)	<0.001
Log-transformed daily ethanol intake, mean	2.4	2.1			0.88 (0.86–0.89)	<0.001
Stroke	n=312 675	n=41 038				
Occupational class						
Blue-collar industry						
Blue-collar	40.1	43.0	1.00		1.00	
Service	12.1	11.3	0.94 (0.90–0.98)	0.004	0.93 (0.89–0.97)	0.001
Professional	3.2	2.4	0.77 (0.70–0.85)	<0.001	0.77 (0.70–0.85)	<0.001
Manager	4.0	3.6	0.91 (0.85–0.97)	0.005	0.88 (0.83–0.95)	<0.001
Service industry						
Blue-collar	4.0	4.5	1.08 (1.02–1.15)	0.01	1.08 (1.02–1.15)	0.01
Service	15.1	16.2	1.02 (0.98–1.06)	0.30	1.01 (0.98–1.05)	0.47
Professional	0.9	0.9	0.97 (0.85–1.10)	0.59	0.99 (0.87–1.13)	0.89
Manager	2.0	2.0	0.98 (0.90–1.06)	0.60	0.96 (0.89–1.04)	0.36
White-collar industry						
Blue-collar	2.1	1.9	0.88 (0.81–0.95)	0.002	0.87 (0.80–0.95)	0.001
Service	8.6	7.2	0.81 (0.77–0.85)	<0.001	0.81 (0.78–0.86)	<0.001
Professional	6.7	6.0	0.85 (0.81–0.89)	<0.001	0.87 (0.83–0.91)	<0.001
Manager	1.3	1.1	0.84 (0.74–0.96)	0.01	0.84 (0.73–0.95)	0.01
Log-transformed pack-year, mean	1.9	2.1			1.08 (1.07–1.09)	<0.001
Log-transformed daily ethanol intake, mean	2.1	2.2			1.07 (1.06–1.08)	<0.001
Overall	n=999 976	n=128 615				
Occupational class						
Blue-collar industry						
Blue-collar	35.8	37.2	1.00		1.00	

Continued

Table 4. Continued

Characteristics	Control %*	Case, %*	Odds Ratio (95% CI)			
			Model 1 [†]	P Value	Model 2 [‡]	P Value
Service	13.0	12.4	0.99 (0.96–1.01)	0.18	0.98 (0.96–1.00)	0.05
Professional	3.7	3.1	0.89 (0.85–0.93)	<0.001	0.90 (0.86–0.93)	<0.001
Manager	4.0	3.9	1.01 (0.98–1.05)	0.46	1.00 (0.96–1.03)	0.84
Service industry						
Blue-collar	4.0	4.3	1.04 (1.00–1.08)	0.05	1.04 (1.00–1.08)	0.05
Service	16.4	17.7	1.06 (1.03–1.08)	<0.001	1.05 (1.03–1.07)	<0.001
Professional	0.9	0.9	1.01 (0.94–1.09)	0.74	1.03 (0.96–1.10)	0.43
Manager	2.0	2.0	1.03 (0.98–1.08)	0.31	1.01 (0.96–1.06)	0.60
White-collar industry						
Blue-collar	2.1	2.0	0.97 (0.93–1.02)	0.25	0.97 (0.93–1.02)	0.24
Service	9.4	8.4	0.90 (0.88–0.92)	<0.001	0.91 (0.88–0.93)	<0.001
Professional	7.4	6.9	0.91 (0.89–0.94)	<0.001	0.94 (0.92–0.97)	<0.001
Manager	1.4	1.2	0.91 (0.85–0.98)	0.01	0.91 (0.85–0.98)	0.01
Log-transformed pack-year, mean	1.9	2.1			1.09 (1.08–1.09)	<0.001
Log-transformed daily ethanol intake, mean	2.2	2.2			1.02 (1.02–1.03)	<0.001

*Estimated with 5 imputed data. Percentage may not total 100 because of multiple imputation and rounding. The characteristics of all variables statistically differed between the case and controls ($P < 0.05$ for t test or Chi-squared test in an imputed data set).

[†]Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.

[‡]Additional adjustment for smoking and alcohol consumption.

prior analysis (data not shown). We mainly focused on the longest-held jobs, which meant less possibility of misclassification of occupational class compared with the current/most recent jobs.^{23,24,27}

Covariates

Confounding factors included sex, age, admission date, and admitting hospital, controlled by exact matching

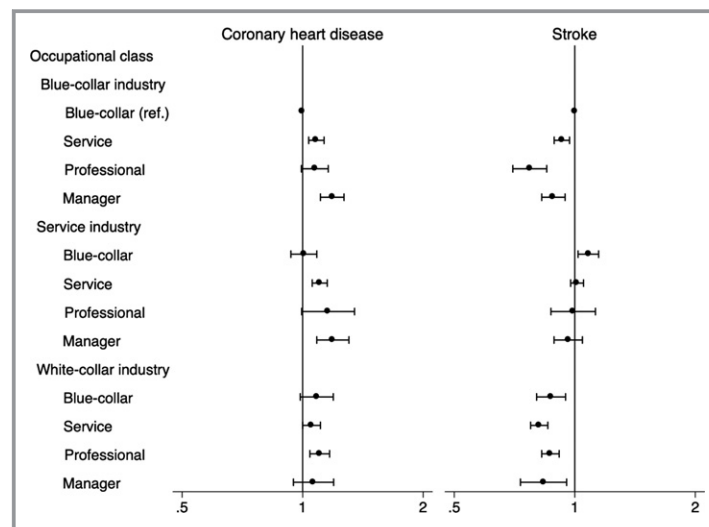


Figure 2. Risk for coronary heart disease and stroke incidence associated with occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 27 452 and 226 378 for coronary heart disease and 41 038 and 312 675 for stroke.

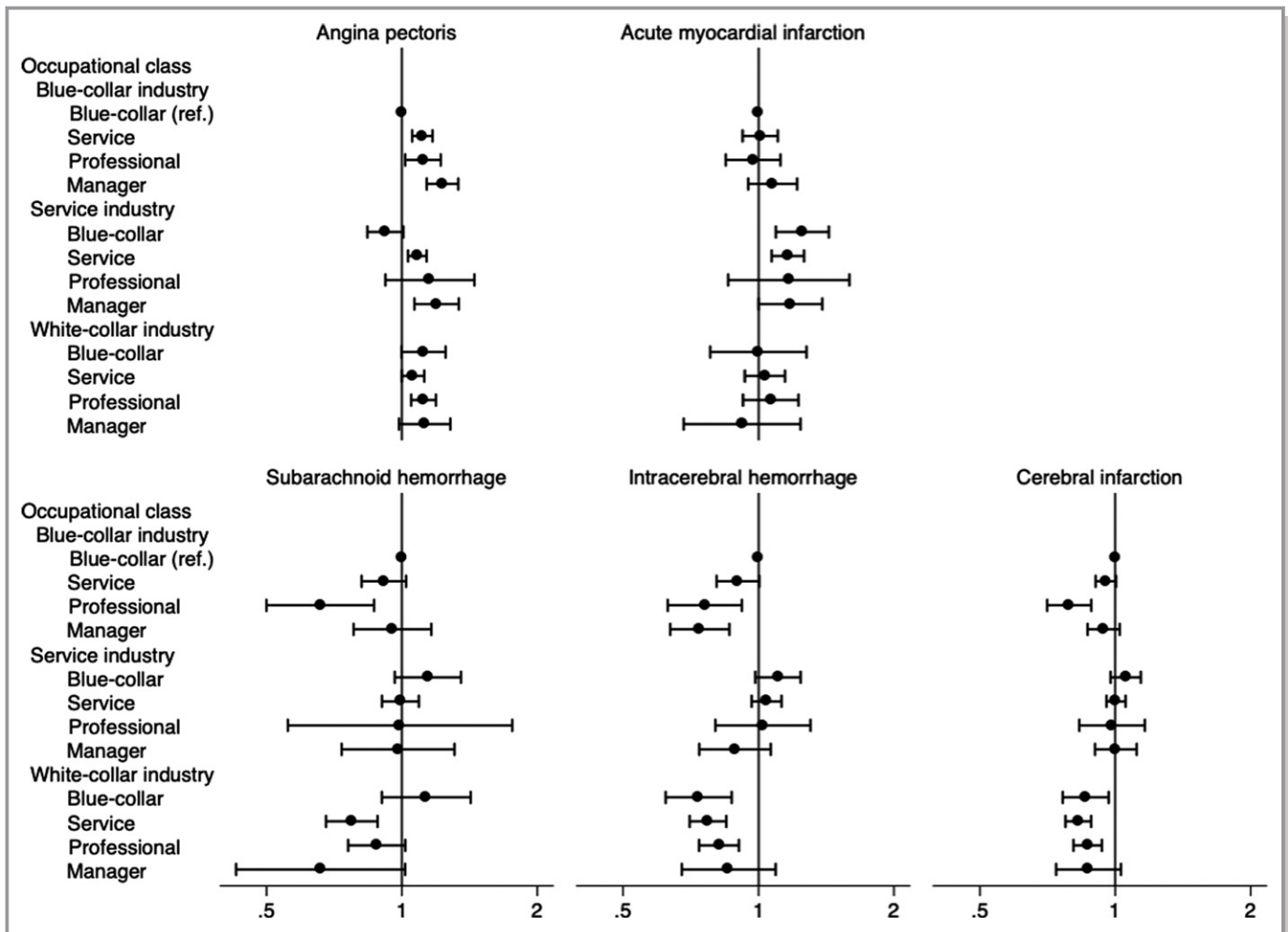


Figure 3. Odds ratios associated with occupational class for incidence of angina pectoris, acute myocardial infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 19 781 and 163 736 for angina pectoris, 7671 and 62 642 for acute myocardial infarction, 4704 and 36 535 for subarachnoid hemorrhage, 10 245 and 79 321 for intracerebral hemorrhage, and 22 242 and 168 286 for cerebral infarction.

procedure.^{23–27} To control for potential changes in diagnosis and treatment as well as regional variations in lifestyle behaviors (such as salt intake) over time, we created dummies for admission date and admitting hospital. Smoking (log-transformed pack-years) and alcohol consumption (log-transformed ethanol gram per day) were included in the regression models as potential mediating variables.^{23–27}

Statistical Analysis

We conducted multiple imputation for missing data among the 1 128 591 study subjects, using all variables in the present study with Multiple Imputation by Chained Equations method;²⁹ and 5 imputed data sets were generated.^{23,24,27,30}

Overall 20% of respondents had missing data, and we performed multiple imputation for the following missing data because of the background differences between those with complete and incomplete data (Table 2): occupational class (n=68 181, 6.0%), smoking (n=107 157, 9.5%), and alcohol consumption (n=209 965, 18.6%).

Odds ratios (ORs) and 95% CIs of CHD, stroke, and overall CVD incidence were estimated by conditional logistic regression with multiple imputation. Blue-collar workers in blue-collar industries served as the referent group for all analyses. Cases were matched to controls based on sex, age, admission date, and admitting hospital (model 1).^{23,24,27,30} Smoking and alcohol consumption were additionally adjusted in model 2.^{23,24,27,30} In addition, ORs and 95% CIs for specific types of CHD and stroke (angina pectoris, AMI, subarachnoid

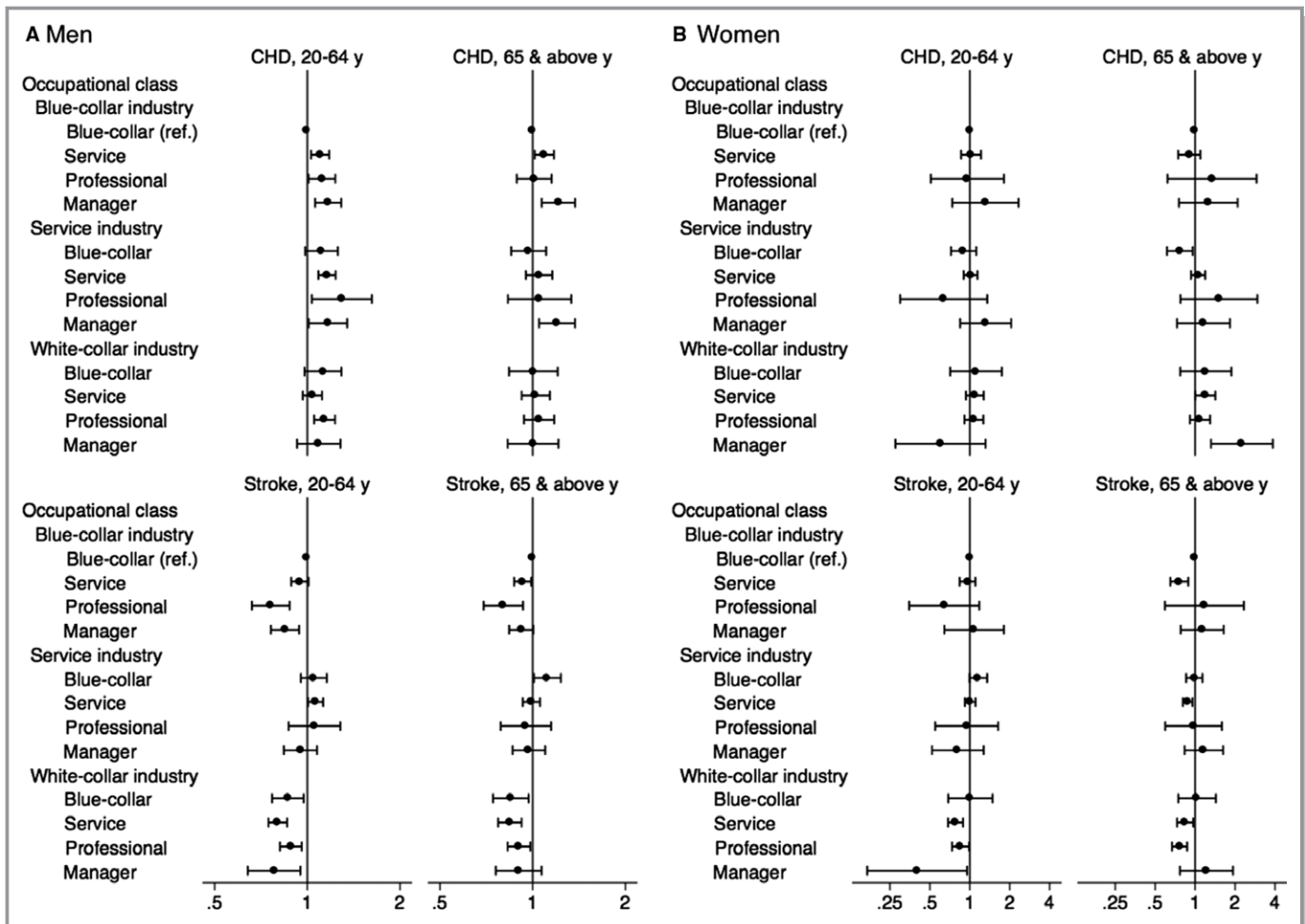


Figure 4. Occupational class gradients stratified by sex and age. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, (A) for men, 13 797 and 118 423 for CHD in 20 to 64 years, 8897 and 74 520 for CHD in ≥ 65 years, 17 240 and 143 109 for stroke in 20 to 64 years, 14 609 and 110 515 for stroke in ≥ 65 years; (B) for women, 2546 and 18 472 for CHD in 20 to 64 years, 2212 and 14 963 for CHD in ≥ 65 years, 4170 and 29 298 for stroke in 20 to 64 years, 5019 and 29 753 for stroke in ≥ 65 years. CHD indicates coronary heart disease.

hemorrhage, intracerebral hemorrhage, and cerebral infarction) were estimated separately.

In sensitivity analyses, we performed stratified analysis with sex (men versus women) and age (20–64 versus ≥ 65 years).³¹ Additionally, to explore potential heterogeneity introduced by secular changes in diagnostic practices or treatment, we performed stratified analysis according to admission period (1984–2002 versus 2003–2016).^{25,27} To check for potential selection bias in hospital controls, alternative control groups (all benign diseases) were applied. To check for potential bias on the matching process, a lower matching ratio (4 controls per each case) was applied. We also assessed the association between the most recent jobs and risk of CVD, assigning the most recent occupational class as the occupational exposure.

Alpha was set at 0.05, and all *P* values were 2-sided. Data were analyzed using STATA/MP13.1 (StataCorp LP, College Station, TX).

Results

The background distribution of the cases and controls are shown in Table 3. Most of the distributions differed between the cases and controls, including occupational class.

Compared with blue-collar workers in blue-collar industries, higher occupational class (professionals and managers) was associated with an excess risk for CHD (Table 4). Even after controlling for smoking and alcohol consumption, the elevated odds remained statistically significant across all industries, being most pronounced in service industries (OR in

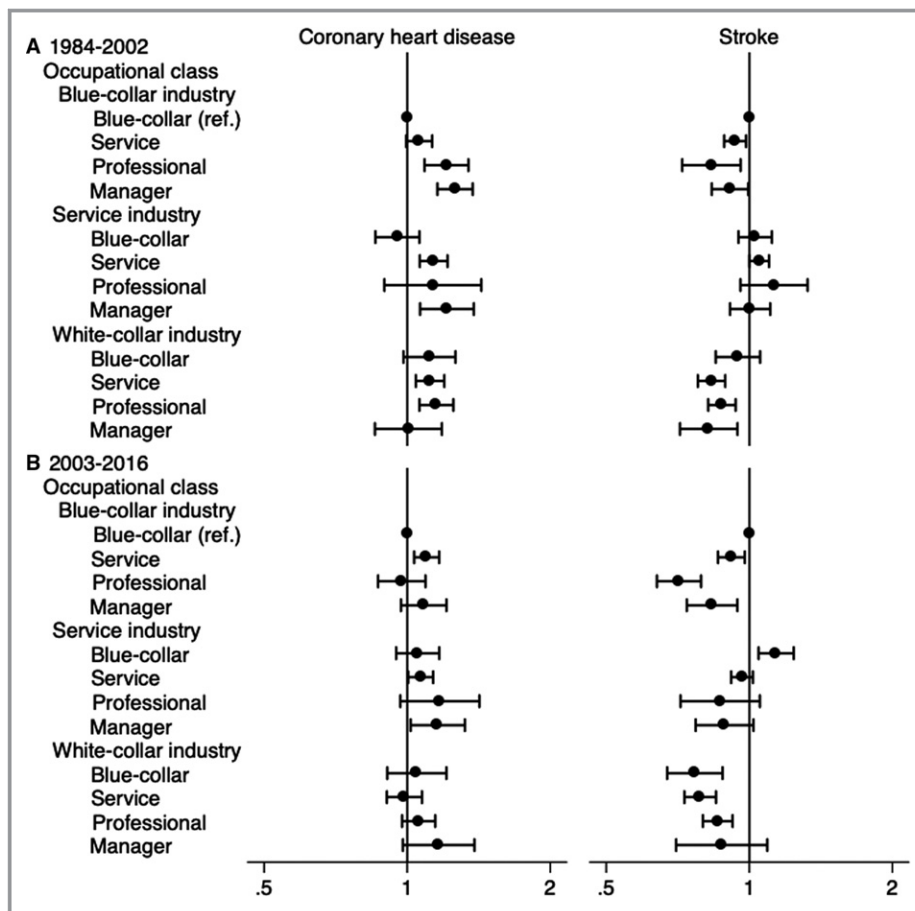


Figure 5. Occupational class gradients stratified by admission period. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, (A) for 1984–2002, 14 170 and 117 229 for coronary heart disease and 24 205 and 184 525 for stroke; (B) for 2003–2016, 13 282 and 109 149 for coronary heart disease and 16 833 and 128 150 for stroke.

managers, 1.19; 95% CI 1.08–1.31; model 2, Figure 2 and Table 4). In the strata of high-occupational classes (managers and professionals) in blue- and white-collar industries, the odds for angina pectoris were elevated, while the odds for acute myocardial infarction were shifted toward the null association (Figure 3 and Table 4). However, in service industries, the odds in that high-occupational status remained elevated for both angina pectoris and myocardial infarction (Figure 3 and Table 4).

By contrast, compared with blue-collar workers in blue-collar industries, higher occupational class was associated with a reduced risk for stroke incidence (Table 4). The protective associations ranged from 0.77 for professionals working in blue-collar industries to 0.88 for managers working in blue-collar industries (model 2, Figure 2 and Table 4). These patterns were repeated for specific subtypes of stroke: subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction (Figure 3).

As a whole, higher occupational class was weakly associated with reduced risk for overall CVD incidence (Table 4), suggesting that the excess risk of CHD among managers/professionals was offset by reduced risk for stroke. In sensitivity analyses, the results stratified by sex and age (Figure 4) and admission period (Figure 5), as well as the results estimated with alternative hospital controls (Figure 6), showed almost the same socioeconomic patterns. The odds ratios estimated with a lower matching ratio (4 controls per case, Table 5), as well as the odds ratios estimated with the most recent occupational class (Figure 7 and Table 6), also showed the same socioeconomic pattern.

Discussion

The direction of association between occupational class and CHD incidence in Japan appears to be opposite to the pattern observed in contemporary Western countries.^{2,4–7} In addition,

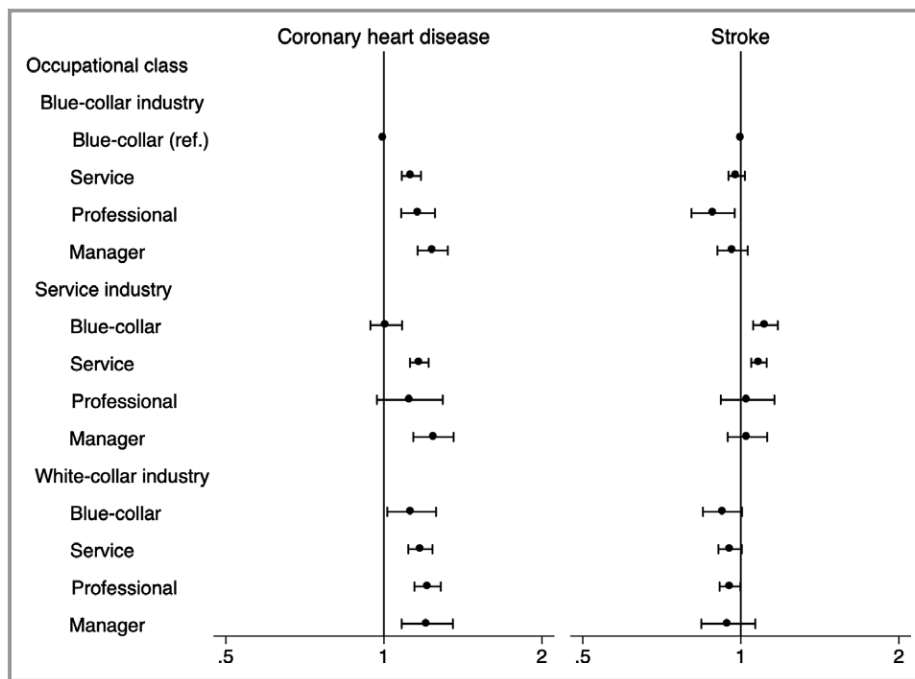


Figure 6. Odds ratio in each occupational class for coronary heart disease and stroke incidence estimated with alternative control groups. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The control group comprised patients diagnosed with benign neoplasm (10.0%), digestive disease (14.4%), endocrine disease (3.5%), eye and ear disease (9.9%), genitourinary system disease (8.3%), infectious disease (2.7%), injury (15.8%), mental disease (0.7%), musculoskeletal disease (15.6%), nerve system disease (3.7%), respiratory disease (6.8%), skin diseases (1.4%), symptoms and ill-health conditions (2.1%), or other diseases such as congenital malformations (3.6%). The numbers of cases and controls used for analysis were, respectively, 22 553 and 220 909 for coronary heart disease and 32 021 and 306 689 for stroke.

we have demonstrated for the first time the opposite directions of socioeconomic gradients for 2 major CVDs, ie, CHD and stroke, within the same country, which suggests excess risk of CHD may be offset by reduced risk of stroke. Furthermore, smoking and alcohol consumption did not fully explain the observed socioeconomic inequalities in Japan, where national strategies that include high-quality cardiovascular prevention and treatment has been provided irrespective of socioeconomic status.¹⁶

As concluded in a recent systematic review of studies in Western countries,⁷ cardiovascular risk factors are strongly patterned by SES, including occupational class, such that socioeconomically advantaged groups enjoy lower CVD risk. However, this socioeconomic “gradient” is not an immutable phenomenon over history. Indeed during the first half of the twentieth century, when chronic disease incidence and mortality was on the rise, CHD was identified as a disease of affluence (as depicted in terms such as “the executive coronary”),¹⁵ and early descriptions of CHD among higher occupational classes date as far back as Osler in 1910.³²

Over the course of the twentieth century, the socioeconomic gradient in CHD reversed, reflecting advances in our understanding of the risk factors for CHD (such as smoking, regular exercise, diet, as well as treatment for high blood pressure and dyslipidemia), and the more rapid adoption of these behaviors by the socioeconomically advantaged classes.¹⁵

Our finding of a reverse gradient by occupational class for coronary disease in Japan may buck this trend. Part of the reason for the observed pattern may be because of the persistently high rates of smoking (by Western standards) even among professionals/managers in Japan, as well as the high rates of heavy drinking in Japanese corporate culture.^{21,22} Nevertheless, our results could not be completely explained by controlling for smoking and drinking habits, suggesting that other cardiovascular risk factors, such as insufficient physical activity, hypertension, diabetes mellitus, and obesity, may play a role.^{7,13} For example, the lowest levels of physical activity and higher prevalence of hypertension were reported among higher occupational class in Japan.^{33,34}

Table 5. Odds Ratios of Each Occupational Class Associated With Risk for Coronary Heart Disease and Stroke Estimated With 4 Matched Controls Per Each Case

Occupational Class	Odds Ratio (95% CI)*			
	Coronary Heart Disease		Stroke	
	Model 1 [†]	Model 2 [‡]	Model 1 [†]	Model 2 [‡]
Blue-collar industry				
Blue-collar	1.00	1.00	1.00	1.00
Service	1.08 (1.04–1.14)	1.08 (1.03–1.13)	0.94 (0.89–0.98)	0.93 (0.89–0.97)
Professional	1.06 (0.98–1.14)	1.08 (1.00–1.17)	0.77 (0.70–0.85)	0.77 (0.70–0.85)
Manager	1.19 (1.11–1.28)	1.19 (1.11–1.28)	0.91 (0.85–0.98)	0.89 (0.83–0.95)
Service industry				
Blue-collar	1.01 (0.93–1.09)	1.01 (0.93–1.09)	1.07 (1.01–1.14)	1.07 (1.01–1.14)
Service	1.10 (1.05–1.15)	1.10 (1.05–1.15)	1.03 (0.99–1.07)	1.02 (0.98–1.06)
Professional	1.08 (0.92–1.27)	1.11 (0.94–1.30)	0.94 (0.83–1.08)	0.96 (0.84–1.10)
Manager	1.21 (1.10–1.34)	1.21 (1.10–1.33)	1.01 (0.93–1.10)	0.99 (0.91–1.08)
White-collar industry				
Blue-collar	1.03 (0.93–1.14)	1.05 (0.95–1.16)	0.88 (0.81–0.96)	0.87 (0.80–0.95)
Service	1.03 (0.98–1.09)	1.05 (1.00–1.11)	0.82 (0.78–0.86)	0.82 (0.78–0.86)
Professional	1.04 (0.98–1.11)	1.09 (1.03–1.16)	0.84 (0.80–0.88)	0.86 (0.82–0.91)
Manager	1.06 (0.93–1.20)	1.07 (0.95–1.22)	0.84 (0.74–0.97)	0.84 (0.73–0.96)

*Estimated with 5 imputed data. The numbers of cases and controls used for analysis were, respectively, 27 452 and 104 391 for coronary heart disease and 41 038 and 152 037 for stroke.

[†]Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.

[‡]Additional adjustment for smoking and alcohol consumption.

Among neighboring East-Asian countries, eg, South Korea, metabolic syndrome has also been reported to be more prevalent in higher occupational classes.³⁵ In addition, emerging workplace-related concerns of long working hours and job stress for cardiovascular risk may also play a role.^{9,36,37} Higher occupational class individuals, particularly in service industries in Japan, are likely vulnerable to stress stemming from striving to meet customer expectations, which sometimes has led to well-publicized instances of death from overwork (“karoshi”).²³

Although CHD and stroke are considered to share major conventional risk factors such as smoking,^{7,8,13,14} notably, the pattern of occupational class gradients for CHD and stroke were in the opposite direction, ie, lower stroke risk among managers/professionals. The opposing patterns of the occupational gradient for CHD and stroke suggest that the 2 diseases have different origins, despite sharing several major risk factors (such as smoking and hypertension). For example, early life course socioeconomic status may also partly play a role in the reduced risk of stroke incidence among higher occupational classes via chronic *Helicobacter pylori* infection.^{13,38,39} The prevalence of *H. pylori* infection is high in the general population in Japan (≈70%),^{40,41} yet studies have

linked earlier acquisition with more disadvantaged childhood socioeconomic circumstances (related to sanitation, overcrowding, rural residence).^{13,38,39} Chronic *H. pylori* infection has been linked with chronic vascular inflammation, which increases the risk for stroke incidence.³⁹

Some limitations should be noted in the present study. First, selection of hospital controls is potentially subject to bias (either toward or away from the null association). However, our sensitivity analysis using alternative control groups (all benign diseases) yielded almost identical results. Additionally, the distribution of occupational classes in the ICD-R data parallels the Japanese national data.^{23,24,27} Although hospital case-control studies are not representative of the national population (thereby limiting external generalizability), internal validity is maintained by sampling the controls from the same source population that sought treatment in the selected hospitals. Our matching procedure was not able to generate 10 controls for every case, which resulted in residual statistical differences in the baseline characteristics between the cases and controls. Although relatively minor, these differences may have nonetheless resulted in some residual confounding. Second, other relevant socioeconomic factors, ie, educational attainment and income

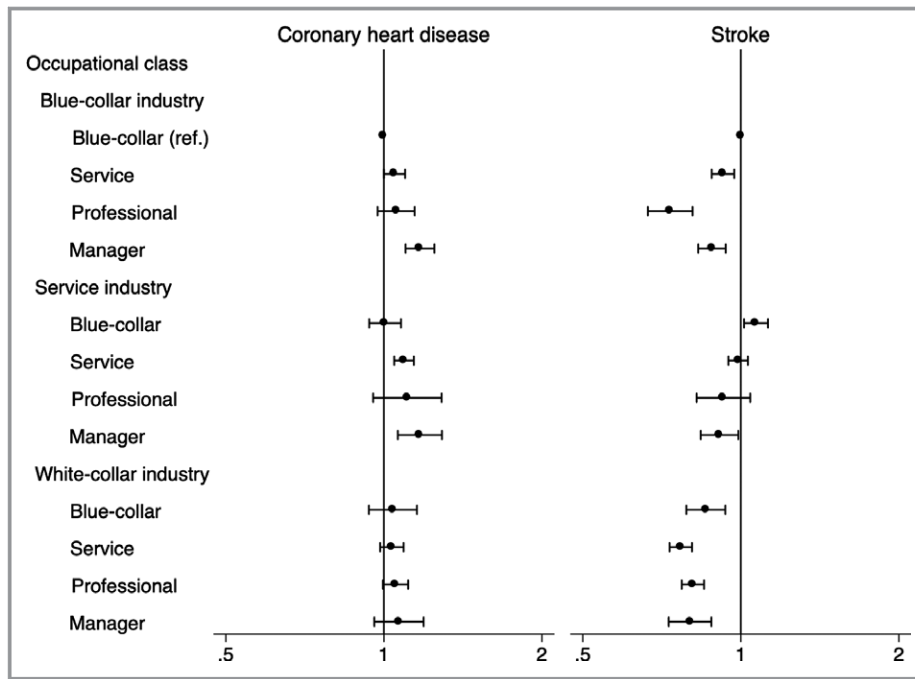


Figure 7. Risks of coronary heart disease and stroke incidence associated with most recent occupational class. The odds ratio (dot) and 95% CI (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, admission date, and admitting hospital, additionally adjusted for smoking and alcohol consumption. The numbers of cases and controls used for analysis were, respectively, 27 306 and 225 227 for coronary heart disease and 40 793 and 310 901 for stroke.

Table 6. Odds Ratios of Most Recent Occupational Class Associated With Risk for Coronary Heart Disease and Stroke

Occupational Class	Odds Ratio (95% CI)*			
	Coronary Heart Disease		Stroke	
	Model 1 [†]	Model 2 [‡]	Model 1 [†]	Model 2 [‡]
Blue-collar industry				
Blue-collar	1.00	1.00	1.00	1.00
Service	1.05 (1.01–1.10)	1.05 (1.00–1.10)	0.93 (0.89–0.98)	0.92 (0.88–0.97)
Professional	1.03 (0.95–1.12)	1.05 (0.97–1.14)	0.73 (0.67–0.81)	0.73 (0.67–0.81)
Manager	1.17 (1.10–1.24)	1.17 (1.10–1.25)	0.90 (0.85–0.96)	0.88 (0.83–0.94)
Service industry				
Blue-collar	1.01 (0.94–1.08)	1.01 (0.94–1.08)	1.07 (1.02–1.13)	1.07 (1.01–1.13)
Service	1.10 (1.05–1.14)	1.09 (1.05–1.14)	0.99 (0.95–1.04)	0.99 (0.95–1.03)
Professional	1.07 (0.92–1.25)	1.11 (0.95–1.29)	0.90 (0.80–1.02)	0.93 (0.82–1.04)
Manager	1.18 (1.07–1.30)	1.17 (1.06–1.29)	0.93 (0.86–1.01)	0.91 (0.84–0.99)
White-collar industry				
Blue-collar	1.02 (0.92–1.14)	1.04 (0.94–1.16)	0.86 (0.79–0.93)	0.86 (0.79–0.93)
Service	1.02 (0.97–1.08)	1.04 (0.98–1.09)	0.77 (0.73–0.81)	0.77 (0.73–0.81)
Professional	1.01 (0.95–1.06)	1.05 (1.00–1.11)	0.79 (0.75–0.83)	0.81 (0.77–0.85)
Manager	1.05 (0.94–1.17)	1.07 (0.96–1.19)	0.80 (0.73–0.88)	0.80 (0.73–0.88)

*Estimated with 5 imputed data. The numbers of cases and controls used for analysis were, respectively, 27 306 and 225 227 for coronary heart disease and 40 793 and 310 901 for stroke.

[†]Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.

[‡]Additional adjustment for smoking and alcohol consumption.

levels,² were not assessed because of the limitations of our data set. However, in previous studies based in Japan, cardiovascular risk was not strongly patterned by education and income levels.^{42,43} Third, our data set did not enable us to assess the severity of disease at admission, other conventional risk factors, such as hypertension, diabetes mellitus, obesity, and physical activity,^{7,13} nor workplace-related risk factors, such as long working hours and job stress.^{9,36,37} In addition, we could not assess the background differences among those admitted to the hospitals with work-related CVD or not. Despite these limitations, the strengths of the present study include a large sample size, one of the largest studies conducted for evaluating the association between occupational class and cardiovascular risk in non-Western settings,⁴² and the longest-held occupational class, which may introduce less misclassification.^{23,24,27} Therefore, future studies incorporating these limitations, including overtime work, are warranted to understand further how the occupation is associated with the observed socioeconomic patterns in cardiovascular and cerebrovascular health.

Conclusion

In conclusion, the Japanese managerial/professional class appeared to potentially experience higher CHD risk compared with other groups, and their overall life expectancy might not be higher than lower occupational classes. There are some specific causes of death in which managers/professionals have higher mortality—eg, suicide.⁴⁴ This pattern appears to reflect the higher prevalence of work-related stress in higher status occupations.²³ Moreover, when we look at overall mortality, the Japanese pattern may buck the trend seen in other developed (Western) societies where high SES groups enjoy a health advantage.^{45,46} Our findings may be a potential exception to the theory of “SES as a fundamental cause of disease” advanced by Link and Phelan, ie, no matter the specific pattern of disease in society at any particular point in time, high SES groups still manage to enjoy an overall health advantage.⁴⁷

Author Contributions

Masayoshi Zaitzu: Conceptualization, funding acquisition, resources, formal analysis, writing—original draft, and writing—review and editing. Soichiro Kato: Conceptualization, writing—review and editing. Yongjoo Kim: Writing—review and editing. Takumi Takeuchi: Resources and writing—review and editing. Yuzuru Sato: Writing—review and editing. Yasuki Kobayashi: Funding acquisition, supervision, and writing—review and editing. Ichiro Kawachi: Conceptualization, supervision, and writing—review and editing.

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Disclosures

None.

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