



Working Hours and Risk of Acute Myocardial Infarction and Stroke Among Middle-Aged Japanese Men

— The Japan Public Health Center-Based Prospective Study Cohort II —

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Background: Evidence from prospective cohort studies regarding the relationship between working hours and risk of cardiovascular disease is limited

Methods and Results: The Japan Public Health Center-Based Prospective Study Cohort II involved 15,277 men aged 40–59 years at the baseline survey in 1993. Respondents were followed up until 2012. During the median 20 years of follow up (257,229 person-years), we observed 212 cases of acute myocardial infarction and 745 stroke events. Cox proportional hazards models adjusted for sociodemographic factors, cardiovascular risk factors, and occupation showed that multivariable-adjusted hazard ratios (HRs) associated with overtime work of ≥ 11 h/day were: 1.63 (95% confidence interval [CI] 1.01–2.63) for acute myocardial infarction and 0.83 (95% CI 0.60–1.13) for total stroke, as compared with the reference group (working 7 to <9 h/day). In the multivariable model, increased risk of acute myocardial infarction associated with overtime work of ≥ 11 h/day was more evident among salaried employees (HR 2.11, 95% CI 1.03–4.35) and men aged 50–59 years (HR 2.60, 95% CI 1.42–4.77).

Conclusions: Among middle-aged Japanese men, working overtime is associated with a higher risk of acute myocardial infarction.

Key Words: Acute myocardial infarction; Cohort studies; Risk factors; Stroke; Working hours

Working long hours is associated with risk of cardiovascular disease. A recent meta-analysis involving studies from Europe, the United States, and Australia showed that long working hours were associated with a higher risk of coronary artery disease and stroke, as compared with standard working hours.¹ The Organization for Economic Cooperation and Development (OECD) reported that working hours in Japan has fallen below the OECD average working hours since 1998² because of the increased proportion of part-time workers.^{3,4} However, deaths from cardiovascular events due to working overtime are recognized as a serious social issue in Japan. Such

deaths are officially certified as work-related deaths, that is, *karoshi*. The Labour Standards Bureau of Japan's Ministry of Health, Labour and Welfare reported that the number of work-related cardiovascular events peaked in 2007 (392 cases) and remained at ~ 300 cases/year from 2008 to 2015.³

Two Japanese case-control studies reported significant associations between longer working hours (≥ 60 h/week or more than 11 h/day) and increased risk of acute myocardial infarction and stroke; however, those studies found that there was also increased risk associated with shorter working hours (≤ 40 h/week or ≤ 7 h/day).^{5,6} The increased risk associated with shorter working hours may be attributed to the

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reversal of cause and effect.^{5,6} In contrast, two Japanese prospective cohort studies with relatively small sample sizes ($\leq 1,600$ participants) and short follow-up periods (≤ 6 years) found no significant association between working hours and risk of cardiovascular disease.^{7,8}

When assessing risk in relation to cardiovascular events, it is necessary to take into account changes in working hours during the follow-up period. To assess this, we used a model that included working hours and potential confounders as time-dependent variables. We hypothesized that: (1) working overtime could be associated with higher risk of acute myocardial infarction and stroke compared with standard working hours; (2) this association may be more evident for salaried employees than for non-salaried employees because long working hours are likely to be accompanied by greater job demands and less job control;⁹ and (3) this association may be more evident at older ages than younger ages because long working hours are likely to be accompanied by greater physical and mental stress for older workers than for younger ones. We tested these hypotheses in a large cohort of middle-aged Japanese men.

Methods

Study Population and Data Retrieval for Analysis

The Japan Public Health Center-Based Prospective (JPHC) Study Cohort II is an ongoing community-based cohort study that started in 1993 and encompasses six public health center (PHC) areas. Details of the JPHC study design have been published elsewhere.¹⁰ In Japan, the PHC is a local government facility (single administrative unit) that is responsible for public health matters. Participants ($n=63,216$) from one PHC area (Osaka) were excluded from the present study because follow-up data were unavailable. The total study population comprised residents of the five included PHC areas who were aged 40–69 years at the time of the baseline survey in 1993. There were 52,256 respondents (24,805 men, 27,451 women), giving an 82.7% response rate. We excluded women from the present analysis because the average working hours for women (4.00 h/day) were approximately half the average for men (8.11 h/day).¹¹ We also excluded men who: were non-Japanese or moved before the study began ($n=11$); reported a history of cancer, coronary artery disease, or stroke at baseline ($n=1,048$); did not have adequate information on their working hours ($n=1,692$); were aged 60–69 years ($n=6,500$), because Japanese employees typically retired at age 60 years at the time of the baseline survey; and those who were unemployed or homemakers ($n=277$). Therefore, the population for the present study comprised 15,277 men. This study was approved by the Institutional Review Board of the National Cancer Center Japan and Osaka University.

Baseline and Follow-up Surveys

Self-administered questionnaires were distributed to all residents at baseline (1993–1994) and at 5- (1998) and 10-year (2003) follow ups. Respondents reported the following demographic characteristics: height; weight; medical history (including hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, and cancer); smoking and drinking habits; and diet. Incomplete answers were supplemented by information acquired through telephone interviews.¹² Informed consent was obtained before respondents completed the questionnaire or from community leaders rather than from the individuals themselves. The latter was

a common informed consent practice in Japan at the time of the baseline survey.

Working hours were determined by items in the baseline (“How long [number of hours] do you work per day?”), 5-year follow-up (“Choose your working hour category from the following: <5 h/day, 5 to <9 h/day, or ≥ 9 h/day”), and 10-year follow-up questionnaires (“Choose your working hours category from the following: <1 h/day, 1 to <3 h/day, 3 to <5 h/day, 5 to <7 h/day, 7 to <9 h/day, 9 to <11 h/day, or ≥ 11 h/day”). We did not use the 5-year follow-up questionnaire because the middle category (5 to <9 h/day) included participants with both fewer than standard working hours (5 to <7 h/day) and standard working hours (7 to <9 h/day). Using the baseline and 10-year follow-up questionnaires, we categorized working hours as: shorter working hours (<7 h/day), reference group (7 to <9 h/day), 1–2 h of overtime work (9 to <11 h/day), and ≥ 3 h of overtime work (≥ 11 h/day) because there was a small number of cases in the <1 h/day, 1 to <3 h/day, and 3 to <5 h/day working hours categories. Shorter working hours included work hours on weekdays that amounted to less than three-quarters of a full-time job (mostly 40 h/week) according to Japan’s Industrial Safety and Health Act and Employees’ Pension Insurance Law.^{13,14} Overtime working included work hours on weekdays that exceeded standard working hours; Japan’s Labor Standards Law defines the maximum working time as 8 h/day.¹⁵ As for basic statistics, we used data from the response to the question “Have you changed your job during the past 5 years?” in both the 5- and 10-year follow-up surveys.

Confirmation of Acute Myocardial Infarction and Stroke Incidence

Details of the methods used for recording acute myocardial infarction and stroke have been published elsewhere.¹⁶ In brief, 50 registered hospitals in the five PHC areas were included in surveillance for acute myocardial infarction and stroke. Registered hospital workers or PHC physicians (blinded to lifestyle data) reviewed the medical records. Acute coronary and stroke events were registered if they occurred after the return date of the baseline questionnaire and before 1 January 2013.

Acute myocardial infarction was confirmed in the medical records according to the Monitoring Trends and Determinants of Cardiovascular Disease project criteria, which require evidence from electrocardiograms, cardiac biomarkers, or autopsy.¹⁷ A probable diagnosis was made if there was typical chest pain, but no such workup was performed. For cases with typical prolonged chest pain (>20 min) without confirmation by electrocardiogram or cardiac enzyme studies, the diagnosis was recorded as possible myocardial infarction and grouped together with myocardial infarction cases. Stroke was confirmed in accordance with the National Survey of Stroke criteria,¹⁸ which require a constellation of neurological deficits with sudden or rapid onset lasting at least 24 h, or until death. For each type of stroke (e.g., hemorrhagic [subarachnoid or intraparenchymal] stroke), a definite diagnosis was established based on examination of computed tomography scans, magnetic resonance images, or autopsy.¹⁹ Sudden cardiac death was defined as death of unknown origin that occurred within 1 h of the event onset. Total cardiovascular disease included acute myocardial infarction, sudden cardiac death, and total stroke. Only first-ever cardiovascular events during follow up were included in the analyses.

Table 1. Cardiovascular Risk Characteristics According to Working Hours at Baseline and at 10-Year Follow up

Working hours (h/day)	Baseline				10-year follow up			
	<7	7 to <9	9 to <11	≥11	<7	7 to <9	9 to <11	≥11
No. of participants	694	6,596	5,945	2,042	4,095	4,994	2,484	1,099
Age, years	51.2±6.1 [‡]	48.9±5.9	48.5±5.8 [‡]	48.1±5.7 [‡]	61.9±5.5 [‡]	57.6±5.5	56.6±5.2 [‡]	55.7±4.9 [‡]
Body mass index, kg/m²	24.1±3.3 [‡]	23.8±3.0	23.6±2.9 [*]	23.8±3.0	23.8±3.0	23.8±3.0	23.7±2.9	23.9±2.9
History of hypertension	126 (18)	1,087 (16)	928 (16)	297 (15)	1,136 (28) [‡]	956 (19)	382 (15) [‡]	156 (14) [‡]
History of diabetes mellitus	60 (9)	421 (6)	325 (5)	118 (6)	280 (7) [‡]	231 (5)	94 (4)	36 (3)
History of hyperlipidemia	20 (3)	206 (3)	197 (3)	61 (3)	236 (6) [‡]	182 (4)	88 (4)	36 (3)
Alcohol consumption								
Never	161 (25) [‡]	1,082 (18)	898 (16)	345 (18)	629 (17) [‡]	656 (16)	283 (15)	124 (15)
Former	25 (4)	164 (3)	115 (2)	53 (3)	309 (9) [‡]	169 (4)	88 (5)	32 (4)
<300 g/week	256 (40) [‡]	3,317 (55)	3,195 (58) [‡]	1,043 (55)	1,562 (43)	1,815 (45)	877 (46)	408 (48)
≥300 g/week	197 (31) [‡]	1,492 (25)	1,265 (23)	460 (24)	1,128 (31)	1,434 (35)	655 (34)	285 (34)
Smoking status								
Never	190 (28)	1,661 (25)	1,514 (26)	491 (24)	1,189 (30) [‡]	1,204 (27)	512 (25) [‡]	228 (25)
Former	120 (17)	1,250 (19)	1,177 (20)	426 (21)	1,208 (31) [‡]	1,182 (27)	590 (29)	257 (28)
Current	376 (55)	3,633 (56)	3,219 (55)	1,110 (55)	1,540 (39) [‡]	2,031 (46)	918 (45) [‡]	431 (47)
Walking or standing								
<1 h/day	96 (14)	1,016 (16)	706 (12) [‡]	238 (12) [‡]	1,736 (48) [‡]	1,659 (41)	704 (39) [‡]	355 (43)
1–3 h/day	203 (29) [‡]	1,595 (24)	1,347 (23)	413 (20) [‡]	1,150 (32) [‡]	1,032 (26)	544 (30)	226 (27)
≥3 h/day	391 (57)	3,932 (60)	3,863 (65) [‡]	1,381 (68) [‡]	758 (21) [‡]	1,309 (33)	555 (31) [‡]	248 (30) [*]
Sleep duration, h/day	7.5±1.4	7.4±1.1	7.4±1.0 [‡]	6.9±1.2 [‡]	7.2±1.1 [*]	7.2±1.0	7.0±1.0 [‡]	6.7±1.0 [‡]
Same job as the one held at baseline at the 5-year follow up	–	–	–	–	1,820 (70) [‡]	1,268 (82)	500 (85)	170 (86)
Same job during the past 5 years	–	–	–	–	1,966 (51) [‡]	3,460 (84)	1,686 (85)	784 (86)
Occupation								
Salaried employee	129 (19) [‡]	3,944 (60)	3,196 (54) [‡]	858 (42) [‡]	306 (11) [‡]	1,743 (42)	881 (46) [‡]	464 (52) [‡]
Agriculture, forestry and fishery worker	269 (40) [‡]	851 (13)	817 (14)	375 (18) [‡]	1,058 (38) [‡]	561 (13)	220 (12)	80 (9) [‡]
Self-employee	172 (25) [‡]	966 (15)	1,044 (18) [‡]	513 (25) [‡]	623 (22) [‡]	777 (19)	370 (19)	142 (16)
Professional worker	20 (3)	239 (4)	165 (3) [*]	48 (2) [‡]	115 (4) [‡]	340 (8)	144 (8)	74 (8)
Multiple occupational worker	78 (11) [‡]	501 (8)	663 (11) [‡]	231 (11) [‡]	322 (12)	509 (12)	210 (11)	94 (11)
Unclassified worker	13 (2) [‡]	29 (0.4)	17 (0.3)	6 (0.3)	232 (8) [‡]	262 (6)	76 (4) [‡]	40 (4)
Homemaker	Excluded	Excluded	Excluded	Excluded	4 (0.1) [*]	0 (0)	0 (0)	0 (0)
Unemployed	Excluded	Excluded	Excluded	Excluded	129 (5) [‡]	0 (0)	0 (0)	0 (0)

Data are presented as mean±SD or number (%), unless otherwise stated. –, no data; Excluded, excluded homemakers and unemployed at baseline. *P<0.05, †P<0.01, and ‡P<0.001, tested for difference from 7 to <9 h/day working hours.

Statistical Analysis

Statistical analyses were based on incidence rates of acute myocardial infarction or stroke from 1993 to the first incidence, other outcomes (death or relocation), or the end of 2012, whichever came earlier. We calculated mean values and proportions for selected cardiovascular risk factors for each working hour category using analysis of covariance. Associations between these categories and risk of acute myocardial infarction and stroke were examined using Cox proportional hazards regression models, including time-dependent variates at the baseline and 10-year follow-up surveys.²⁰ The follow up for each participant was divided into 2 time periods (from baseline to 10-year follow up, and from 10-year follow up to end of follow up) to take retirement into account. For each time period, a separate Cox analysis was carried out, and weighted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Three models were constructed with progressive adjustment for potential confounders. The first model was adjusted for baseline age (years). The second model was also adjusted for body mass index (BMI) (kg/m²), history of hypertension

(yes, no), history of diabetes mellitus (yes, no), history of hyperlipidemia (yes, no), smoking status (never, former, current), alcohol intake (never, former, <300 g [alcohol]/week, ≥300 g/week), walking or standing time (<1 h/day, 1 to <3 h/day, ≥3 h/day), and sleep duration (hours). The third model was further adjusted for occupation (salaried employee, agriculture/forestry/fishery worker, self-employed, professional worker, multiple occupational worker, unclassified occupational worker, homemaker, and unemployed). For the sensitivity analysis accounting for the competing risk of death, the Fine and Gray model was used to estimate subhazard ratios of acute myocardial infarction and total stroke.²¹ Furthermore, we conducted the analysis by excluding acute myocardial infarction and stroke events that took place in the first 3 years of follow up to examine the reverse causation, as in a previous meta-analysis.¹

We performed stratification by occupation (salaried employees and non-salaried workers) and age (40–49 and 50–59 years). Interaction terms were generated by multiplying each category of working hours (h/day) by dichotomous stratification of occupation and age, and were added

	Working hours (h/day)				P for trend*
	<7	7 to <9	9 to <11	≥11	
Person-years	43,460	106,503	78,257	29,008	
No. at risk at baseline	694	6,596	5,945	2,042	
No. at risk at 10-year survey	4,095	4,994	2,484	1,099	
Acute myocardial infarction					
No. of cases	50	76	58	28	
Age-adjusted HR (95% CI)	1.09 (0.74–1.61)	1.00	1.14 (0.81–1.61)	1.52 (0.98–2.34)	0.07
Multivariable-adjusted HR (95% CI) [†]	1.23 (0.82–1.85)	1.00	1.23 (0.85–1.77)	1.66 (1.04–2.64)	0.05
Multivariable-adjusted HR (95% CI) [‡]	1.29 (0.81–2.05)	1.00	1.22 (0.84–1.77)	1.63 (1.01–2.63)	0.07
Sudden cardiac death					
No. of cases	8	12	10	1	
Age-adjusted HR (95% CI)	1.20 (0.45–3.21)	1.00	1.22 (0.52–2.84)	–	0.66
Multivariable-adjusted HR (95% CI) [†]	1.21 (0.45–3.27)	1.00	1.02 (0.41–2.52)	–	0.71
Multivariable-adjusted HR (95% CI) [‡]	1.11 (0.34–3.56)	1.00	1.08 (0.43–2.73)	–	0.68
Total stroke					
No. of cases	209	283	194	59	
Age-adjusted HR (95% CI)	1.13 (0.93–1.37)	1.00	1.04 (0.87–1.25)	0.88 (0.67–1.17)	0.26
Multivariable-adjusted HR (95% CI) [†]	1.10 (0.89–1.35)	1.00	1.05 (0.86–1.28)	0.85 (0.62–1.15)	0.21
Multivariable-adjusted HR (95% CI) [‡]	1.04 (0.82–1.32)	1.00	1.06 (0.87–1.29)	0.83 (0.60–1.13)	0.21
Hemorrhagic stroke					
No. of cases	73	118	91	21	
Age-adjusted HR (95% CI)	1.06 (0.77–1.46)	1.00	1.14 (0.86–1.50)	0.72 (0.45–1.15)	0.15
Multivariable-adjusted HR (95% CI) [†]	1.00 (0.71–1.40)	1.00	1.15 (0.86–1.54)	0.62 (0.37–1.06)	0.08
Multivariable-adjusted HR (95% CI) [‡]	1.07 (0.73–1.56)	1.00	1.20 (0.89–1.62)	0.64 (0.37–1.09)	0.08
Ischemic stroke					
No. of cases	135	164	103	37	
Age-adjusted HR (95% CI)	1.15 (0.90–1.48)	1.00	0.98 (0.76–1.25)	0.98 (0.69–1.41)	0.73
Multivariable-adjusted HR (95% CI) [†]	1.15 (0.88–1.50)	1.00	0.97 (0.74–1.27)	1.00 (0.68–1.47)	0.84
Multivariable-adjusted HR (95% CI) [‡]	1.00 (0.73–1.37)	1.00	0.96 (0.73–1.26)	0.95 (0.64–1.41)	0.79
Total cardiovascular disease					
No. of cases	266	371	262	88	
Age-adjusted HR (95%CI)	1.12 (0.94–1.33)	1.00	1.07 (0.91–1.25)	1.00 (0.79–1.26)	0.75
Multivariable-adjusted HR (95% CI) [†]	1.12 (0.94–1.35)	1.00	1.08 (0.91–1.28)	0.99 (0.77–1.28)	0.74
Multivariable-adjusted HR (95% CI) [‡]	1.09 (0.88–1.34)	1.00	1.09 (0.92–1.30)	0.97 (0.75–1.25)	0.69

HR, hazard ratio; CI, confidence interval; –, not determined due to the small number of case. *Calculated among ≥7 h/day workers. †Adjusted further for body mass index, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, smoking, alcohol consumption, hours of walking or standing, and sleep duration (h). ‡Adjusted further for occupation.

to the Cox proportional hazards model to assess interactions. The proportional hazard assumption was tested using the logarithm of the follow-up periods (<10 and ≥10 years) by working hours; it was not violated for acute myocardial infarction ($P=0.30$ for <10 years and 0.18 for ≥10 years, respectively) or for total stroke ($P=0.94$ for <10 years and 0.56 for ≥10 years, respectively). SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. All probability values for statistical tests were 2-sided, and $P<0.05$ was regarded as statistically significant.

Results

Table 1 shows the mean values and proportions of respondents' cardiovascular risk characteristics by working hours at baseline ($n=15,277$) and at the 10-year follow up ($n=12,672$). The proportions of participants in the working hour groups at baseline were: 4.5% in the <7 h/day group, 43.2% in the 7 to <9 h/day group (standard working hours,

reference), 38.9% in the 9 to <11 h/day group, and 13.4% in the ≥11 h/day group. Men with ≥3 h of overtime work (≥11 h/day) were younger, had longer hours (≥3 h/day) of walking or standing, and shorter sleep duration (hours) than those who worked standard hours. Men who worked shorter hours were older, had higher mean BMI, and more likely to consume more alcohol (≥300 g/day) than those who worked standard hours. The proportions of participants in the working hour groups at the 10-year follow-up survey were: 32.3% in the <7 h/day group, 39.4% in the 7 to <9 h/day group, 19.6% in the 9 to <11 h/day group, and 8.7% in the ≥11 h/day group. Men who worked ≥11 h/day (≥3 h of overtime) were younger, had the lower prevalence of hypertension history, and had shorter sleep duration than those who worked standard hours. Men who worked shorter hours were older, had higher prevalence hypertension histories, diabetes and hyperlipidemia, lower prevalence of being a current smoker, shorter hours (<1 h/day) of walking or standing, and longer sleep duration than

Table 3. Multivariable-Adjusted HRs and 95% CIs of Acute Myocardial Infarction According to Working Hours, Stratified by Occupation and Age Groups

	Working hours (h/day)				P for trend*
	<7	7 to <9	9 to <11	≥11	
Salaried employees					
Person-years	4,018	52,059	37,700	12,070	
No. at risk at baseline	129	3,944	3,196	858	
No. at risk at 10-year survey	306	1,743	881	464	
No. of cases	8	33	27	10	
Multivariable-adjusted HR (95% CI) [†]	2.49 (1.12–5.56)	1.00	1.46 (0.87–2.46)	2.11 (1.03–4.35)	0.08
Non-salaried employees					
Person-years	27,895	47,037	35,122	15,062	
No. at risk at baseline	552	2,586	2,706	1,173	
No. at risk at 10-year survey	2,483	2,449	1,020	430	
No. of cases	29	34	25	14	
Multivariable-adjusted HR (95% CI) [†]	1.25 (0.73–2.13)	1.00	1.11 (0.65–1.90)	1.48 (0.78–2.81)	0.31
Age, 40–49 years					
Person-years	13,720	63,116	48,632	19,573	
No. at risk at baseline	260	3,580	3,386	1,226	
No. at risk at 10-year survey	1,212	3,235	1,807	878	
No. of cases	10	30	28	10	
Multivariable-adjusted HR (95% CI) [†]	1.03 (0.45–2.34)	1.00	1.24 (0.71–2.15)	0.94 (0.42–2.10)	0.87
Age, 50–59 years					
Person-years	29,740	43,387	29,625	9,435	
No. at risk at baseline	434	3,016	2,559	816	
No. at risk at 10-year survey	2,883	1,759	677	221	
No. of cases	40	46	30	18	
Multivariable-adjusted HR (95% CI) [†]	1.52 (0.85–2.71)	1.00	1.25 (0.75–2.07)	2.60 (1.42–4.77)	0.004

HR, hazard ratio; CI, confidence interval. *Calculated among ≥7h/day workers. [†]Adjusted for age, body mass index, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, smoking, alcohol consumption, hours of walking or standing, and sleep duration (hours). [‡]Adjusted further for occupation.

those who worked standard hours.

At the 5-year follow-up survey of 12,672 men aged 45–64 years, the proportions of participants who had kept the same job since baseline (5 years earlier) in line with their working hour group of <7h/day, 7 to <9h/day, 9 to <11h/day, and ≥11h/day were 70%, 82%, 85%, and 86% respectively. At the 10-year follow up of 12,672 men aged 50–69 years, these corresponding proportions were 51%, 84%, 85%, and 86% respectively. Only 5% of them were unemployed.

During the median 20-year follow up, we observed 212 cases of acute myocardial infarction and 745 stroke events. **Table 2** presents the age- and multivariable-adjusted HRs for cardiovascular diseases according to working hours. Men who worked ≥11h/day tended to have a higher risk of acute myocardial infarction than those who worked standard hours. This association was statistically significant after adjustment for cardiovascular risk factors and occupation. No such trends were observed for other outcomes. In the competing risk model, the results were similar; the subhazard ratios for acute myocardial infarction were 1.61 (95% CI 0.68–3.84) for <7h/day, 1.29 (95% CI 0.81–2.04) for 9 to <11h/day, and 1.77 (95% CI 0.97–3.23) for ≥11h/day; those for total stroke were 0.83 (95% CI 0.47–1.44) for <7h/day, 1.13 (95% CI 0.88–1.46) for 9 to <11h/day, and 0.83 (95% CI 0.55–1.25) for ≥11h/day. When we repeated the analyses, excluding incident cases during the first 3 years of follow up, the results were not altered significantly; the

HRs were 1.23 (95% CI 0.76–2.00) for <7h/day, 1.10 (95% CI 0.73–1.67) for 9 to <11h/day, and 1.83 (95% CI 1.13–2.97) for ≥11h/day.

Table 3 shows the multivariable-adjusted HRs of acute myocardial infarction according to working hours, stratified by occupation and age group. The increased risk of acute myocardial infarction associated with working ≥11h/day and <7h/day was more evident among salaried employees than non-salaried employees, although the interaction by occupation was not statistically significant (P for interaction=0.97). The increased risk of acute myocardial infarction associated with working ≥11h/day tended to be confined to older ages (50–59 years), but the interaction did not reach statistical significance (P for interaction=0.13). Furthermore, taking retirement into account, we performed stratification analyses using a combination of age (40–49 and 50–59 years) and follow-up periods (<10 and ≥10 years). Among older participants (aged 50–59 years), the HRs of acute myocardial infarction within the first 10 years were 2.44 (95% CI 0.93–6.39) for <7h/day, 1.66 (95% CI 0.89–3.09) for 9 to <11h/day, and 3.03 (95% CI 1.42–6.46) for ≥11h/day; the HRs for ≥10 years were 1.24 (95% CI 0.61–2.51), 0.71 (95% CI 0.24–2.12) and 2.20 (95% CI 0.74–6.58) respectively. In contrast, no such trend was observed for younger ages; the HRs of acute myocardial infarction within the first 10 years were 0.65 (95% CI 0.08–5.16) for <7h/day, 0.99 (95% CI 0.48–2.04) for 9 to <11h/day, and 0.79 (95% CI 0.26–2.42) for ≥11h/day; the

HRs for ≥ 10 years were 1.13 (95% CI 0.43–2.93), 1.58 (95% CI 0.68–3.66), and 1.30 (95% CI 0.41–4.07) respectively, among the younger age groups.

Discussion

In this large, long-term cohort study involving middle-aged men, with a median follow up of 20 years, we found that working ≥ 11 h/day was associated with increased risk of acute myocardial infarction but not of stroke. Furthermore, the increased risk associated with working ≥ 11 h/day was more evident among salaried employees and men aged 50–59 years.

Our finding regarding acute myocardial infarction was consistent with the results of previous meta-analyses, whereas our results for stroke were not.^{1,22,23} A meta-analysis involving 6 case-control and 5 cohort studies reported that working ≥ 60 h/week was associated with increased risk of cardiovascular disease, including acute myocardial infarction and stroke, with an odds ratio of 1.37 (95% CI 1.11–1.70), in comparison with working < 40 h/week.²³ Another meta-analysis, including 4 cohort studies and comparing long working hours with standard working hours as defined in each study, found an association between long working hours and risk of coronary artery disease, with a relative risk of 1.39 (95% CI 1.12–1.72).²² A more recent meta-analysis of 25 large cohort studies showed that working long hours (≥ 45 h/week in 5 published studies, ≥ 55 h/week in 20 unpublished studies) was associated with increased relative risks of coronary artery disease (1.13, 95% CI 1.02–1.26) and stroke (1.33, 95% CI 1.11–1.61) compared with working standard hours.¹ However, that meta-analysis did not include the results of 2 Japanese cohort studies.^{1,7,8} A 3.7-year cohort study of 797 white-collar Japanese workers aged 20–60 years found no significant association between long working hours (≥ 50 h/week) and risk of incident cardiovascular disease (hypertension, ischemic heart diseases, intracerebral hemorrhage, cerebral infarction, cerebral atherosclerosis, and atherosclerosis) in comparison with reference working hours (< 50 h/week), with a relative risk of 1.26 (95% CI 0.59–2.69).⁸ Another 7-year follow-up study of 908 Japanese men aged 40–65 years with hypertension also found no significant association between long working hours (≥ 10 h/day) and risk of incident cardiovascular disease (cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, myocardial infarction, heart failure, aortic aneurysmal rupture, or sudden death) as compared with the reference (< 10 h/day): multivariable-adjusted HR 1.45 (95% CI 0.67–3.14).⁷ However, these 2 studies did not follow participants after retirement and had low statistical power owing to a small number of cardiovascular disease cases (12 for ≥ 50 h/week and 11 for ≥ 10 h/day).

Our finding of no association between long working hours and risk of total stroke was inconsistent with the results of a previous meta-analysis showing that working long hours (≥ 11 h/day) was associated with greater risk of total stroke, with a multivariable-adjusted relative risk of 1.33 (95% CI 1.11–1.61).¹ The lack of an association in our study is considered to be owing to the lower proportion of thromboembolic infarction in Japanese ($\sim 25\%$)²⁴ than Caucasian ($\sim 50\%$) populations;^{25,26} the effect of long working hours may be stronger for thromboembolic stroke as well as acute myocardial infarction, in which atherosclerosis of large arteries is the basic pathology.²⁷ Long working hours

has been associated with major atherosclerosis risk factors such as hypertension,²⁸ diabetes mellitus,²⁹ and hypercholesterolemia.³⁰ The prospective Kuopio Ischemic Heart Disease Risk Factor Study involving Finnish men aged 42–60 years found that work time (days/week or h/year) was positively associated with the progression of carotid atherosclerosis,³¹ a strong risk factor for acute myocardial infarction^{32,33} and thromboembolic stroke.^{34,35}

The excess risk of acute myocardial infarction associated with long working hours among salaried employees in the present study was consistent with the results of previous studies. Several reports have shown that long working hours (≥ 55 h/week,^{1,36} 41–45 h/week,⁹ and 11–12 h/day³⁷) are associated with increased risk of mortality from cardiovascular disease, compared with standard working hours, among salaried employees,^{1,9,36,37} but not among non-salaried workers.⁹ The Northern Ireland Mortality Study, including 414,949 workers aged 20 to 59 or 64 years (official retirement ages), showed an association between long working hours (≥ 55 h/week) and risk of total cardiovascular disease mortality, compared with the reference group (30–40 h/week), among men with routine occupations; multivariable-adjusted HR of 1.49 (95% CI 1.10–2.00).⁹ However, no associations were observed among managerial/professional male workers, with a multivariable-adjusted HR of 0.95 (95% CI 0.69–1.34), and self-employed men including farmers, with a multivariable-adjusted HR of 0.96 (95% CI 0.72–1.29).⁹ The Whitehall II cohort study of British civil servants aged 31–61 years showed a stronger association between long working hours (11–12 h/day) and risk of coronary artery disease among employees with lower decision latitude (HR 1.78, 95% CI 1.10–2.89) than those with high decision latitude (HR 1.26, 95% CI 0.77–2.04).³⁷ A previous study of 1,198 employees from 5 branches of a manufacturing company in Japan indicated that long working hours (≥ 80 h/week) was associated with increased psychological distress among employees with low job control, but not among those with high job control.³⁸ Thus, the increased risk of acute myocardial infarction among salaried men in the present study may be owing to higher psychosocial job strain (high job demand plus low job control) than among self-employed workers.

The excess risk of acute myocardial infarction associated with fewer working hours (< 7 h/day) among salaried employees could be owing to the presence of preclinical cardiovascular disease or unspecified illness that raises the future risk of myocardial infarction. Some of the salaried employees who work shorter hours may have been forced to work in time-limited jobs because of their illness or poor health conditions of the person. This result was consistent with the findings from previous studies.^{5,6} A case-control study of 526 Japanese men aged 30–69 years showed that short working hours (≤ 7 h/day) as well as long working hours (> 11 h/day), compared with working 7–9 h/day were associated with an increased risk of acute myocardial infarction, with an odds ratios of 3.07 (95% CI 1.77–5.32) and 2.44 (95% CI 1.26–4.73) respectively.⁶ Another case-control study of 1,117 Korean men and women aged 20–65 years showed that those with the longest (> 52 h/week) and shortest (≤ 40 h/week) working hours had increased risk of cardiovascular disease, including acute myocardial infarction, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction, in comparison with the reference work time (40–48 h/week): odds ratios 2.90 (95% CI 1.86–4.52) and 3.46 (95% CI 2.38–5.03) respectively.⁵ However,

the evidence on short working hours is limited in several cohort studies;^{7-9,36,37} they did not examine short working days (<7 h/day³⁷ or <35 h/week^{1,9}) or they used the reference number of hours including both standard and shorter working hours (<10 h/day,⁷ ≤40 h/week,³⁶ or <44 h/week⁸).

A previous meta-analysis with an average follow-up period of 8.5 years showed that the relative risk of coronary artery disease associated with long working hours (≥55 h/week) did not vary between those aged <50 years (1.19, 95% CI 0.91–1.57) and those aged ≥50 years (1.06, 95% CI 0.90–1.24).¹ However, our study found that the excess risk of acute myocardial infarction associated with long working times (≥11 h/day) was confined to men aged 50–59 years and not to those aged 40–49 years. Because the 20-year median follow-up period of our study was much longer than that of the previous meta-analyses, men aged 50–59 years at the baseline survey were re-examined at the 10-year follow up, and then followed up for another median 10 years. A recent cross-sectional study including 3,060 Koreans reported a significant association (odds ratio 2.18, 95% CI 1.07–4.45) of elevated high-sensitivity C-reactive protein (>3.0 mg/L), a risk factor for stroke and ischemic heart disease,³⁹ with long working hours (≥55 h/week) among older (≥60 years) but not younger age groups (<60 years); multivariable-adjusted odds ratio=0.80 (95% CI 0.47–1.38).⁴⁰ That finding suggests that working longer hours lead to a higher risk of acute myocardial infarction among older workers.

In our study, even though some participants retired from their jobs, over 80% of men who worked ≥7 h/day kept the same job and only 5% became unemployed. Furthermore, a significant increased risk of acute myocardial infarction associated with working ≥11 h/day was observed among older aged workers (50–59 years) within the first 10 years, during which time their work responsibilities might have changed after they reached the age of 60 years. Approximately 70% of companies reported setting the retirement age at 60 years in 1993–1994,⁴¹ however, some companies introduced a “continuous employment system” between 1985 and 2000, particularly those companies with fewer than 1,000 employees.⁴¹ Continuous employment of elderly workers (≥60 years) was expanded after revision of the Act on Stabilization and Employment of Elderly Persons in October of 2000.⁴²

The present study results indicated an association between overtime work and an increased risk of acute myocardial infarction among salaried employees and male workers aged 50–59 years at baseline. These findings support future occupational health guidelines for workers aged over 60 years to refrain them from working overtime.

Study Strengths and Limitations

The strengths of the present study include long follow-up time and large sample size, which enabled us to perform stratified analyses by age and occupation. We used the exposure data at 2 time points as time-varying covariates that is working hours and confounding variables in the Cox proportional hazard model, to account for changes in individuals' working hours and confounding variables during the follow-up period.

The present study had several limitations. First, working hours and other variables were self-reported and there might have been measurement errors, however, such errors would be non-differential as they were assessed before any occurrence of the outcomes. Second, although we updated

the information on working hours, some participants might have retired or changed their type of work. The present exposure variable might be a marker of other causal variables associated with working time before such changes occurred. Third, weekly working hours and employment patterns (e.g., full- and part-time work) were not surveyed; therefore, the reported daily working hours might not always represent weekly working hours (e.g., if a person worked 5 days/week, the mean regular working hours would be 8.8 h/day because the mean weekly working hours among Japanese men were reported as 44 h/week).⁴³ Finally, we could not exclude the qualitative aspects of work, such as psychosocial job control and shift work, which might affect the outcomes.

Conclusions

Compared with standard working hours (7 to <9 h/day), working overtime (≥11 h/day) is associated with higher risk of acute myocardial infarction among middle-aged Japanese men.

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Disclosure

The authors declare no conflicts of interest.

References

1. Kivimaki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, et al. Long working hours and risk of coronary heart disease and stroke: A systematic review and meta-analysis of published and unpublished data for 603,838 individuals. *Lancet* 2015; **386**: 1739–1746.
2. The Organisation for Economic Co-operation and Development. Average annual hours actually worked per worker. 2017. <http://stats.oecd.org/> (accessed February 22, 2019).
3. Ministry of Health, Labour and Welfare, Japan. The White Paper on prevention of Karoshi (Death caused by Overwork) (in Japanese). 2016. <http://www.mhlw.go.jp/wp/hakusyo/karoshi/16/dl/16-1.pdf> (accessed February 22, 2019).
4. Ministry of Health, Labour and Welfare, Japan. Current situation in part-time workers (in Japanese). 2006. <http://www.mhlw.go.jp/shingi/2006/07/s0720-3d.html> (accessed February 22, 2019).
5. Jeong I, Rhie J, Kim I, Ryu I, Jung PK, Park YS, et al. Working hours and cardiovascular disease in Korean workers: A case-control study. *J Occup Health* 2014; **55**: 385–391.
6. Sokejima S, Kagamimori S. Working hours as a risk factor for acute myocardial infarction in Japan: Case-control study. *BMJ* 1998; **317**: 775–780.
7. Uchiyama S, Kurasawa T, Sekizawa T, Nakatsuka H. Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: Hypertension follow-up group study. *J Occup Health* 2005; **47**: 102–111.
8. Tarumi K, Hagihara A, Morimoto K. A prospective observation of onsets of health defects associated with working hours. *Ind Health* 2003; **41**: 101–108.
9. O'Reilly D, Rosato M. Worked to death?: A census-based longitudinal study of the relationship between the numbers of hours spent working and mortality risk. *Int J Epidemiol* 2013; **42**: 1820–1830.
10. Tsugane S, Sawada N. The JPHC study: Design and some findings on the typical Japanese diet. *Jpn J Clin Oncol* 2014; **44**:

- 777–782.
11. Statistics Bureau, Ministry of Internal Affairs and Communications, Japan. Survey on time use and leisure activities (in Japanese). 1996. https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00200533&tstat=00000150002&cycle=0&tclass1=000001008790&tclass2=000001015834&survey=%E7%A4%BE%E4%BC%9A%E7%94%9F%E6%B4%BB%E5%9F%BA%E6%9C%AC%E8%AA%BF%E6%9F%BB&result_page=1&second=1&second2=1 (accessed February 22, 2019).
 12. Tsugane S, Sobue T. Baseline survey of JPHC study--design and participation rate: Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. *J Epidemiol* 2001; **11**: S24–S29.
 13. Ministry of Health, Labour and Welfare, Japan. About the enforcement of the revised part-time workers act (in Japanese). 2014. https://www.mhlw.go.jp/web/t_doc_keyword?keyword=%E5%9F%BA%E7%99%BA%E7%AC%AC1001016%E5%8F%B7&dataId=00tc0268&dataType=1&pageNo=1&mode=0 (accessed February 22, 2019).
 14. Ministry of Health, Labour and Welfare, Japan. Extend health insurance and employees' pension insurance to part-time workers (in Japanese). 2016. https://www.mhlw.go.jp/web/t_doc?dataId=00tc1970&dataType=1&pageNo=1 (accessed February 22, 2019).
 15. Ministry of Justice, Japan. Labor Standards Act (in Japanese). 2012. <http://www.japaneselawtranslation.go.jp/law/detail?id=2236&vm=04&re=01&new=1> (accessed February 22, 2019).
 16. Yamagishi K, Iso H, Kokubo Y, Saito I, Yatsuya H, Ishihara J, et al. Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: The JPHC Study. *Eur Heart J* 2013; **34**: 1225–1232.
 17. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**: 583–612.
 18. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke: Clinical findings. *Stroke* 1981; **12**: I13–I44.
 19. Iso H, Rexrode K, Hennekens CH, Manson JE. Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. *Ann Epidemiol* 2000; **10**: 81–87.
 20. Teresa MP, Melissa EB. Your "Survival" guide to using time-dependent covariates. 2012. <http://support.sas.com/resources/papers/proceedings12/168-2012.pdf> (accessed February 22, 2019).
 21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–509.
 22. Virtanen M, Heikkilä K, Jokela M, Ferrie JE, Batty GD, Vahtera J, et al. Long working hours and coronary heart disease: A systematic review and meta-analysis. *Am J Epidemiol* 2012; **176**: 586–596.
 23. Kang MY, Park H, Seo JC, Kim D, Lim YH, Lim S, et al. Long working hours and cardiovascular disease: A meta-analysis of epidemiologic studies. *J Occup Environ Med* 2012; **54**: 532–537.
 24. Kitamura A, Nakagawa Y, Sato M, Iso H, Sato S, Imano H, et al. Proportions of stroke subtypes among men and women > or =40 years of age in an urban Japanese city in 1992, 1997, and 2002. *Stroke* 2006; **37**: 1374–1378.
 25. Bejot Y, Rouaud O, Durier J, Caillier M, Marie C, Freysz M, et al. Decrease in the stroke case fatality rates in a French population-based twenty-year study: A comparison between men and women. *Cerebrovasc Dis* 2007; **24**: 439–444.
 26. Saposnik G, Caplan LR, Gonzalez LA, Baird A, Dashe J, Luraschi A, et al. Differences in stroke subtypes among natives and caucasians in Boston and Buenos Aires. *Stroke* 2000; **31**: 2385–2389.
 27. Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR Jr, et al. Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries: The Akita Pathology Study. *Stroke* 1993; **24**: 954–964.
 28. Yoo DH, Kang MY, Paek D, Min B, Cho SI. Effect of long working hours on self-reported hypertension among middle-aged and older wage workers. *Ann Occup Environ Med* 2014; **26**: 25.
 29. Kivimäki M, Virtanen M, Kawachi I, Nyberg ST, Alfredsson L, Batty GD, et al. Long working hours, socioeconomic status, and the risk of incident type 2 diabetes: A meta-analysis of published and unpublished data from 222 120 individuals. *Lancet Diabetes Endocrinol* 2015; **3**: 27–34.
 30. Virtanen M, Magnusson Hansson L, Goldberg M, Zins M, Stenholm S, Vahtera J, et al. Long working hours, anthropometry, lung function, blood pressure and blood-based biomarkers: Cross-sectional findings from the CONSTANCES study. *J Epidemiol Community Health* 2019; **73**: 130–135.
 31. Krause N, Brand RJ, Kauhanen J, Kaplan GA, Syme SL, Wong CC, et al. Work time and 11-year progression of carotid atherosclerosis in middle-aged Finnish men. *Prev Chronic Dis* 2009; **6**: A13.
 32. Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: The Suita Study. *Arch Intern Med* 2000; **160**: 2297–2303.
 33. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999; **340**: 14–22.
 34. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke* 2004; **35**: 2788–2794.
 35. Leng XY, Chen XY, Chook P, Xiong L, Lin WH, Liu JY, et al. Correlation of large artery intracranial occlusive disease with carotid intima-media thickness and presence of carotid plaque. *Stroke* 2013; **44**: 68–72.
 36. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Long work hours and physical fitness: 30-year risk of ischaemic heart disease and all-cause mortality among middle-aged Caucasian men. *Heart* 2010; **96**: 1638–1644.
 37. Virtanen M, Ferrie JE, Singh-Manoux A, Shipley MJ, Vahtera J, Marmot MG, et al. Overtime work and incident coronary heart disease: The Whitehall II prospective cohort study. *Eur Heart J* 2010; **31**: 1737–1744.
 38. Hino A, Inoue A, Kawakami N, Tsuno K, Tomioka K, Nakanishi M, et al. Buffering effects of job resources on the association of overtime work hours with psychological distress in Japanese white-collar workers. *Int Arch Occup Environ Health* 2015; **88**: 631–640.
 39. Iso H, Noda H, Ikeda A, Yamagishi K, Inoue M, Iwasaki M, et al. The impact of C-reactive protein on risk of stroke, stroke subtypes, and ischemic heart disease in middle-aged Japanese: The Japan Public Health Center-based Study. *J Atheroscler Thromb* 2012; **19**: 756–766.
 40. Lee J, Kim HR. The association between long working hours and high-sensitivity C-reactive protein in older aged individuals: The Korea National Health and Nutrition Examination Survey (KNHANES) 2015. *J Occup Environ Med* 2018; **60**: 775–780.
 41. Asao Y. Trends and issues of employment of older persons and related institutions in Japan (in Japanese). 2014. https://www.jil.go.jp/foreign/report/2014/pdf/2014_0930.pdf (accessed February 22, 2019).
 42. Ministry of Justice, Japan. Act on stabilization of employment of elderly persons (in Japanese). 2012. <http://www.japaneselawtranslation.go.jp/law/detail?id=2621&vm=&re=02> (accessed February 22, 2019).
 43. International Labour Organization. Employment by sex and weekly hours actually worked. 2017. www.ilo.org/ilostat (accessed February 22, 2019).