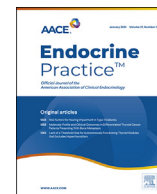




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## Original Article

## Trends in Cardiovascular Risk Factors by Income Among Japanese Adults Aged 30–49 Years From 2017 to 2020: A Nationwide Longitudinal Cohort Study

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## ABSTRACT

**Objective:** Income is a major social determinant of cardiovascular health. However, individual-level evidence regarding the trends in cardiovascular risk factors by income level among young working-age adults is limited. We thus aimed to examine the trends in cardiovascular risk factors among men and women aged 30–49 years by their income levels.

**Methods:** This nationwide longitudinal study included Japanese adults aged 30–49 years, who annually participated in the national health screening program from 2017 to 2020. Modified Poisson regression models were used to investigate trends in the prevalence of cardiovascular risk factors (obesity, hypertension, diabetes, and dyslipidemia) according to tertiles of individuals' annual income, adjusting for potential confounders.

**Results:** Among 58 814 adults, 50 024 (85%) were men; the mean (SD) age was 42.1 (5.4) years. Over the study period, the low-income group consistently showed a higher prevalence of obesity, hypertension, and diabetes than the high-income group. The difference in the prevalence of these diseases, particularly hypertension, across income groups increased from 2017 to 2020 among both men (low-income vs high-income: +5.73% [95% CI, 4.72–6.73] in 2017 and +8.26% [95% CI, 7.11–9.41] in 2020) and women (low-income vs high-income: +2.53% [95% CI, 0.99–4.06] in 2017 and +3.83% [95% CI, 1.93–5.73] in 2020).

**Conclusion:** Among adults aged 30–49 years in Japan, a country with a universal healthcare coverage system, we found an increase in the gap of cardiovascular risk factors by income levels over the last 4 years. Careful monitoring of the increasing social disparities is needed to achieve cardiovascular health equity at this life stage.

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## Introduction

The global incidence of cardiovascular disease (CVD) and its risk factors—such as obesity, hypertension, diabetes, and dyslipidemia—among young adults have increased since 1990.<sup>1–3</sup> In the past 2 decades, the proportion of acute myocardial infarctions attributable to young patients aged 35–54 years has increased from 27% to 32%.<sup>4</sup> Although the cumulative exposure to such CVD risk factors

in young adulthood is associated with CVD outcomes later in life,<sup>5</sup> a previous study showed that younger adults aged 18–31 years had a 33% slower rate of receiving a diagnosis of hypertension (ie, undiagnosed hypertension) than older adults aged ≥60 years.<sup>6</sup>

Reducing social disparities in cardiovascular health has been a public health priority worldwide.<sup>7</sup> There is ample evidence that shows the unequivocal association between low income, one of the major social determinants of health, and CVD risk factors.<sup>8–12</sup> However, these studies are generally based on cross-sectional surveys. Moreover, evidence based on individual-level trends in CVD risk factors across income strata is lacking. Understanding such trends among young working-age individuals by their income levels would help clinicians and decision-makers to develop health policies that eliminate the social disparities in cardiovascular

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health. Although observed disparities in countries such as the United States may be attributable to different affordability for medical care because people enroll in different insurances or are uninsured,<sup>13</sup> this mechanism does not necessarily apply to a country that has a universal healthcare coverage system such as Japan.<sup>14,15</sup> Furthermore, the high-cost medical expense benefit sets limits on out-of-pocket expenses for very expensive medical care, and the limits are set to be lower as income decreases (eg, the limit of monthly out-of-pocket expenses is 57 600 Japanese yen [JPY] [\$524 when 1 US dollar [USD] = 110 JPY] for people whose annual income is less than approximately 3 700 000 JPY [\$33,636]). Therefore, examination of the longitudinal trends in health disparities using data in Japan would provide evidence about the existence of social disparities even when insurance is comprehensively covered.

Using a nationwide cohort with follow-up data, we investigated the relationship between individual income levels and CVD risk factors (obesity, hypertension, diabetes, and dyslipidemia) among adults aged 30–49 years. We then examined the trends in the prevalence of CVD risk factors according to income levels from 2017 to 2020. We also examined the trends in the measurements of these risk factors including body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin A1c (HbA1c), and low-density lipoprotein cholesterol (LDL-C). In Japan, under the Industrial Safety and Health Law, full-time employees are obliged to undergo annual health checkup for free, which allowed us to use individual-level longitudinal data on CVD risk factors among the early working-age population in their 30s and 40s. Given the difference in cardiovascular risk profiles by gender,<sup>16</sup> we conducted all analyses among men and women, separately.

## Methods

### Data Source and Participants

We retrieved nationwide cohort data of adults aged 30–49 year old with annual health screening data between April 2017 and March 2021 (2017/4–2021/3) from the database of the Health Insurance Association for Architecture and Civil Engineering companies—one of the largest employment-based health insurers in Japan. Among the 70 746 eligible participants with annual health screening data in 2017, we included those who had health screening data every year between 2017 and 2020, which resulted in a final analytical sample of 58 814 (83%; [Supplementary Fig. 1](#)). In this young working population from architecture and civil engineering companies, 50 024 (85%) were men and 8790 (15%) were women. This study followed the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology.

### Measurement of Variables

#### Exposure

Information on yearly income, including a bonus for each individual, were obtained from the insurance registry data of 2017, 2018, 2019, and 2020 (JPY was translated to USD at the rate of 1USD = 110 JPY). This data had a low risk of measurement error because individuals made mandatory insurance payments based on income level reported by their employers. In our main analysis, we categorized men and women into three categories based on tertiles of yearly income in 2017. We also calculated the average income between 2017 and 2020 and equivalized income (income divided by the square root of the number of household members<sup>17,18</sup>) in our sensitivity analysis.

## Highlights

- Using a nationwide longitudinal cohort with annual health checkups in Japan, a country with a universal healthcare coverage system, we found social disparities in cardiovascular risk factors (obesity, hypertension, and diabetes) by individual income levels among adults aged 30–49 years.
- The disparities, particularly in the prevalence of hypertension, increased between 2017 and 2020 in both men and women.
- These findings indicate the widening of social disparities in cardiovascular management among the young working-age population.
- They also highlight the importance of careful monitoring of cardiovascular risk factors with socioeconomic information at the individual level to achieve the best attainable cardiovascular health at this life stage even when insurance is comprehensively covered.

## Clinical Relevance

Among adults aged 30–49 years in Japan under universal healthcare coverage system, we found an increase in the gap of cardiovascular risk factors by income levels over the last 4 years. Careful monitoring is needed to prevent the widening of social disparities in cardiovascular health among the young working-age population.

## Outcome

Our primary outcomes were the prevalence of obesity (BMI  $\geq 25$  kg/m<sup>2</sup> based on the definition of the Japan Society for the Study of Obesity,<sup>19</sup> considering the specific distribution of BMI in the Japanese population), hypertension (SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg or taking any antihypertensive medications), diabetes (HbA1c  $\geq 6.5\%$  or taking any antihyperglycemic medications), and dyslipidemia (LDL-C  $\geq 140$  mmHg or taking any lipid-lowering medications).<sup>20–22</sup> Secondary outcomes were BMI, waist circumference, SBP, DBP, HbA1c, and LDL-C levels. During the physical examination in the annual health screening, weight, height, waist circumference, SBP, and DBP were measured by trained staff. BMI was calculated as the weight in kilograms divided by the height in meters squared. Blood samples were collected at the examination center and sent to central laboratories for the measurement of HbA1c and LDL-C levels. Information regarding medication use was self-reported.

## Other Covariates

From the annual health screening data in 2017, we obtained sociodemographic and behavioral information including age (years), gender (men, women), smoking (yes, no), alcohol drinking (yes, no), and exercise more than 30 minutes per day (yes, no). We also extracted the information about the number of household members and geographical information (at the prefecture level) from the insurance registry data.

## Statistical Analyses

We employed multivariable modified Poisson regression models to investigate the difference in the prevalence of CVD risk factors (ie, obesity, hypertension, diabetes, and dyslipidemia)

between low- or middle-income groups and high-income groups in each year from 2017 to 2020. In all models for men and women, we adjusted for age, smoking, alcohol intake, and number of household members, along with regional fixed effects (ie, 47 prefectures) and calculated clustered standard error to consider correlation within individuals. We also included the indicator variable of the year (2017, 2018, 2019, and 2020) and the interaction terms between the income groups and the year indicator variable to assess the trends in the prevalent gap of cardiovascular risk factors across income groups over time. After fitting the regression models, we calculated the predicted prevalence of each CVD risk factor for each observation and averaged over the entire sample using the *margins* command in Stata.<sup>23</sup> We applied the same approach using multivariable ordinary least squares regression models for the measurement of CVD risk factors (BMI, waist circumference, SBP, DBP, HbA1c, and LDL-C).

### Sensitivity Analyses

We conducted the following three sensitivity analyses: First, to minimize the influence of time-varying income during the study period (particularly including the COVID pandemic in 2020), we redefined the income levels using the average annual income between 2017 and 2020, instead of income in 2017. Second, to consider income as an indicator of the economic resources available to a standardized household, we used the equivalized income in 2017. Lastly, to assess sensitivity to the tertile cut-off points of income, we examined the absolute and relative socioeconomic inequalities for each CVD risk factor across the study period using the slope index of inequality and relative index of inequality, respectively (Text S1).<sup>24</sup>

All statistical analyses were conducted using Stata software (version 16.0) and R software (version 4.1.1). Missing data were imputed using a random forest approach.<sup>25</sup> This study was reviewed and accepted by the review board of Kyoto University (IRB#R0817).

## Results

The mean  $\pm$  standard deviation of the age was  $42.1 \pm 5.4$  and men were 85%. Across 50 024 men aged 30–49 years, those in lower-income groups were more likely to be younger and smokers, but they were less likely to drink alcohol, exercise >30 minutes per day, and have a larger number of household members compared to the high-income group in 2017 (Table 1). BMI, waist circumference, SBP, DBP, HbA1c, and LDL-C did not differ by income group, whereas men in the high-income group showed a higher percentage of antihypertensive and lipid-lowering drug use. Similar patterns were observed among women except for a slightly higher prevalence of antihypertensive, antihyperglycemic, and lipid-lowering medication use in the low-income group than in the high-income group.

### *Trends in the Prevalence of Cardiovascular Risk Factors by Income Among Men and Women*

During the study period, all three income groups showed an increase in the prevalence of each cardiovascular risk factor every year between 2017 and 2020 among men (Supplementary Fig. 2) and women (Supplementary Fig. 3). In 2017, we found a higher prevalence of obesity, hypertension, and diabetes among men in the low- or middle-income groups than in the high-income group (Fig. 1 and Supplementary Table 1). The difference in the prevalence of these CVD risk factors across income tertiles, particularly obesity and hypertension, increased from 2017 to 2020; obesity (low-income vs high-income), +1.61% [95% CI, 0.41–2.81] in 2017, +2.29%

[95% CI, 1.07–3.51] in 2018, +2.53% [95% CI, 1.30–3.76] in 2019, and +3.45% [95% CI, 2.21–4.69] in 2020; hypertension (low-income vs high-income), +5.73% [95% CI, 4.72–6.73] in 2017, +6.32% [95% CI, 5.27–7.36] in 2018, +6.67% [95% CI, 5.59–7.75] in 2019, and +8.26% [95% CI, 7.11–9.41] in 2020 (Fig. 1 and Supplementary Table 1). We also found a higher prevalence of dyslipidemia among men in the low- or middle-income groups compared to those in the high-income group during 2019, but this difference was not found in other years.

Compared with women in the high-income group, we found a higher prevalence of hypertension among those in the low- or middle-income groups (Supplementary Table 1). The difference in the prevalence of hypertension across income tertiles among women increased from 2017 to 2020: low-income vs high-income: +2.53% [95% CI, 0.99–4.06] in 2017, +2.28% [95% CI, 0.63–3.93] in 2018, +2.74% [95% CI, 0.99–4.49] in 2019, and +3.83% [95% CI, 1.93–5.73] in 2020.

### *Trends in the Measurement of Cardiovascular Risk Factors by Income Among Men and Women*

We found larger BMI, larger waist circumference, higher SBP, higher DBP, and higher HbA1c levels among men in the low- or middle-income groups compared to those in the high-income group (Fig. 2). This difference increased during the study period. We found no evidence of a difference in LDL-C levels by income tertile over the study period. Similar patterns were found among women, particularly for BMI, waist circumference, and DBP, but the 95% CI was null for most of the adjusted differences due to the limited sample size (Supplementary Fig. 4).

### Sensitivity Analyses

The results did not qualitatively change when i) using the average income between 2017 and 2020 (Supplementary Figs. 5 and 6) and ii) using the equivalised income (Supplementary Figs. 7 and 8) instead of yearly income in 2017. We also found an increase in the slope index of inequality but not in the relative index of inequality for obesity and hypertension between 2017 and 2020, particularly among men (Supplementary Tables 2 and 3), supporting our main findings that the absolute (but not relative) income inequalities for these diseases widened during the study period.

## Discussion

Across young working-age men and women, who underwent the national annual health-screening program between 2017 and 2020 in Japan, we found that low income was associated with a higher prevalence of obesity, hypertension, and diabetes. The differences in the prevalence of these CVD risk factors, particularly hypertension, across income strata have increased over the last 4 years. Increasing trends were also observed for the differences in BMI, waist circumference, SBP, DBP, and HbA1c between the low-income and high-income groups. These findings raise concerns about the widening social inequality in cardiovascular health among the young working-age population.

The present study using nationwide follow-up data on CVD risk factors would advance our current state of knowledge about the role and importance of individual income levels in CVD management. A large previous study in the United States showed that adults with higher income levels had greater life expectancy and the gap in life expectancy between the richest 5% and the poorest 5% of adults increased from 1999 to 2014.<sup>26</sup> Differences in CVD risk factors and CVD death by socioeconomic factors have also been well-

**Table 1**  
Demographic Characteristics of Study Sample in 2017

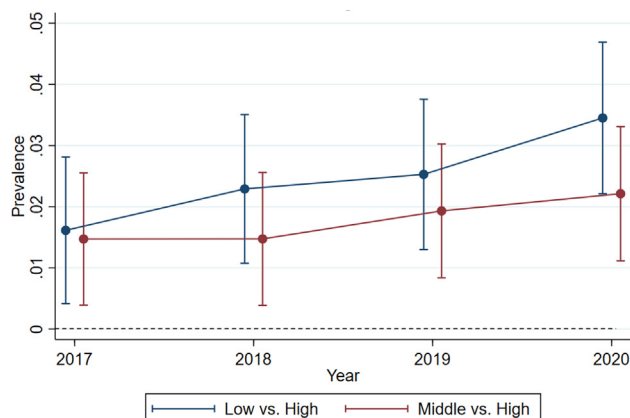
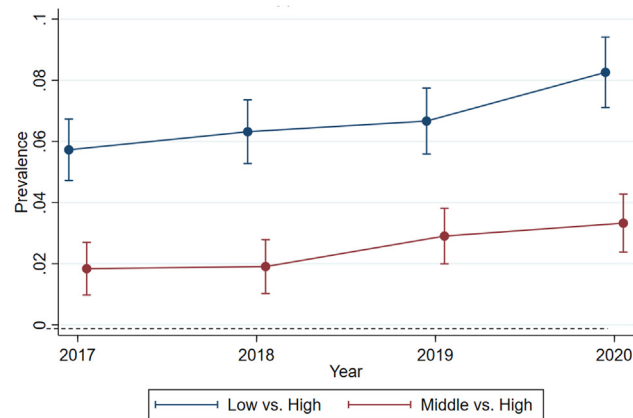
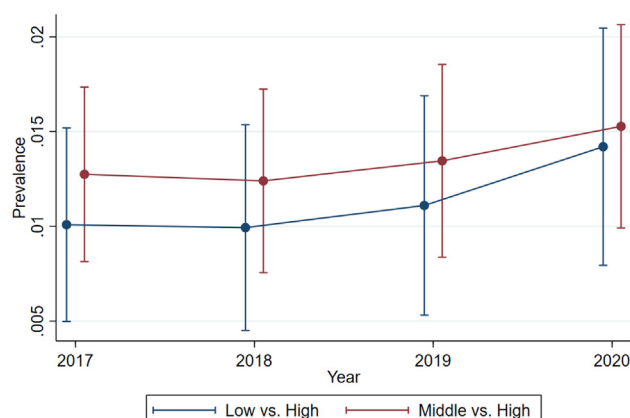
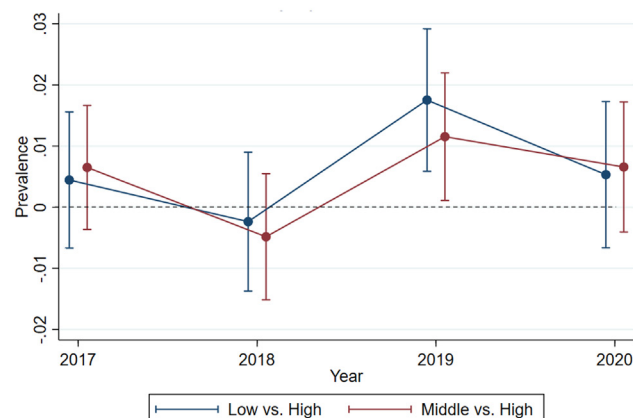
Men	Low-income group N = 16 677	Middle-income group N = 16 674	High-income group N = 16 673
Income			
Range	<\$53,700	\$53,700 to \$74,800	>\$74,800
Mean (SD)	\$42,011 (\$7840)	\$63,883 (\$6052)	\$89,474 (\$1056)
Median (IQR)	\$43,164 (\$11,691)	\$63,818 (\$10,420)	\$88,082 (\$14,000)
Age, mean (SD)	40.4 (5.4)	41.9 (5.4)	44.3 (4.5)
Smoking, %	49.1	38.7	31.0
Missing, %	5.9	3.9	1.5
Alcohol drinking, %	71.8	81.8	86.6
Missing, %	9.3	7.6	12.1
Exercise >30min, %	22.7	20.9	21.4
Missing, %	15.1	11.3	13.2
The number of household members	2.5 (1.4)	2.9 (1.4)	3.3 (1.2)
BMI, kg/m <sup>2</sup> , mean (SD)	24.7 (4.1)	24.6 (3.7)	24.5 (3.4)
Missing, %	<0.1	<0.1	<0.1
Waist circumference, cm, mean (SD)	85.6 (10.5)	85.8 (9.7)	85.6 (8.9)
Missing, %	0.8	0.2	0.4
Systolic blood pressure, mmHg, mean (SD)	124.9 (15.3)	123.6 (14.7)	123.4 (14.2)
Missing, %	<0.1	<0.1	<0.1
Diastolic blood pressure, mmHg, mean (SD)	77.4 (12.0)	77.4 (11.7)	78.1 (11.4)
Missing, %	<0.1	<0.1	<0.1
HbA1c, %, mean (SD)	5.5 (0.7)	5.5 (0.6)	5.5 (0.6)
Missing, %	8.0	3.7	2.0
LDL cholesterol, mg/dl, mean (SD)	123.6 (32.2)	124.0 (30.6)	123.9 (29.7)
Missing, %	0.5	0.1	0.2
Antihypertensive medication use, %	7.2	7.6	8.7
Missing, %	5.4	3.2	0.7
Antihyperglycemic medication use, %	2.8	2.9	2.4
Missing, %	5.4	3.2	0.7
Lipid-lowering medication use, %	4.2	5.0	6.2
Missing, %	5.4	3.2	0.7
Women	Low-income group N = 2930	Middle-income group N = 2930	High-income group N = 2930
Income			
Range	<\$31,420	\$31,420 to \$43,020	>\$43,020
Mean (SD)	\$24,709 (\$4858)	\$36,896 (\$3300)	\$55,316 (\$1105)
Median (IQR)	\$25,673 (\$7118)	\$36,782 (\$5646)	\$51,790 (\$13,991)
Age, mean (SD)	41.1 (5.2)	36.9 (3.3)	43.1 (5.4)
Smoking, %	12.9	8.6	7.6
Missing, %	5.2	5.0	3.7
Alcohol drinking, %	50.4	56.9	64.8
Missing, %	11.2	11.4	12.8
Exercise >30min, %	13.4	15.3	16.0
Missing, %	15.4	13.7	13.9
The number of household members	1.5 (0.9)	1.4 (0.8)	1.3 (0.7)
BMI, kg/m <sup>2</sup> , mean (SD)	22.0 (4.0)	21.8 (3.7)	21.8 (3.6)
Missing, %	0.1	0.1	0.3
Waist circumference, cm, mean (SD)	76.8 (9.9)	76.6 (9.6)	76.9 (9.3)
Missing, %	1.2	0.5	0.8
Systolic blood pressure, mmHg, mean (SD)	114.5 (15.8)	113.6 (15.2)	114.0 (15.3)
Missing, %	<0.1	<0.1	0.3
Diastolic blood pressure, mmHg, mean (SD)	69.8 (11.4)	69.8 (11.2)	70.3 (11.3)
Missing, %	<0.1	<0.1	0.3
HbA1c, %, mean (SD)	5.4 (0.4)	5.3 (0.3)	5.4 (0.4)
Missing, %	6.5	1.9	1.0
LDL cholesterol, mg/dl, mean (SD)	111.9 (29.0)	111.3 (28.4)	113.9 (29.2)
Missing, %	0.4	0.1	0.4
Antihypertensive medication use, %	3.1	2.7	2.4
Missing, %	4.4	4.7	3.1
Antihyperglycemic medication use, %	1.2	0.5	0.5
Missing, %	4.4	4.7	3.1
Lipid-lowering medication use, %	2.1	1.8	1.8
Missing, %	4.4	4.7	3.1

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; IQR = Interquartile range; LDL = Low-density lipoprotein; SD = Standard deviation.

documented.<sup>7–11</sup> For example, a study by He et al<sup>8</sup> reported higher BMI, HbA1c, and 10-year CVD risk score among adults with income-to-poverty ratio (annual household income divided by the poverty threshold with the adjustment of family size and inflation)  $\leq 100\%$  than those with income-to-poverty ratio  $\geq 500\%$  over the last 20 years between 1999 and 2018 in the United States. A study by Zhang et al also reported that low socioeconomic status (defined by household income, employment status, and education levels) was

associated with a higher risk of all-cause mortality (hazard ratio [HR], 2.13), cardiovascular mortality (HR, 2.25), and incident CVD (HR, 1.65) in the United Kingdom.<sup>9</sup> However, these previous studies were based on the repeated cross-sectional study design of national survey data or cohort study design linked to mortality database and thus did not evaluate individual-level trends in CVD risk factors.

Importantly, it is unclear whether this social disparity in cardiovascular health has increased or decreased over the last several

**A** Obesity**B** Hypertension**C** Diabetes**D** Dyslipidemia

**Fig. 1.** Adjusted trends in the difference in the prevalence of cardiovascular risk factors from 2017 to 2020 across income tertiles in 2017 among men. The model adjusted for age, smoking, alcohol intake, and number of household members, along with regional fixed effects and calculated clustered standard error to consider correlation within individuals. We also included the indicator variable of the year (2017, 2018, 2019, and 2020) and the interaction terms between the income groups and the year indicator variable to assess the statistical trends over time.

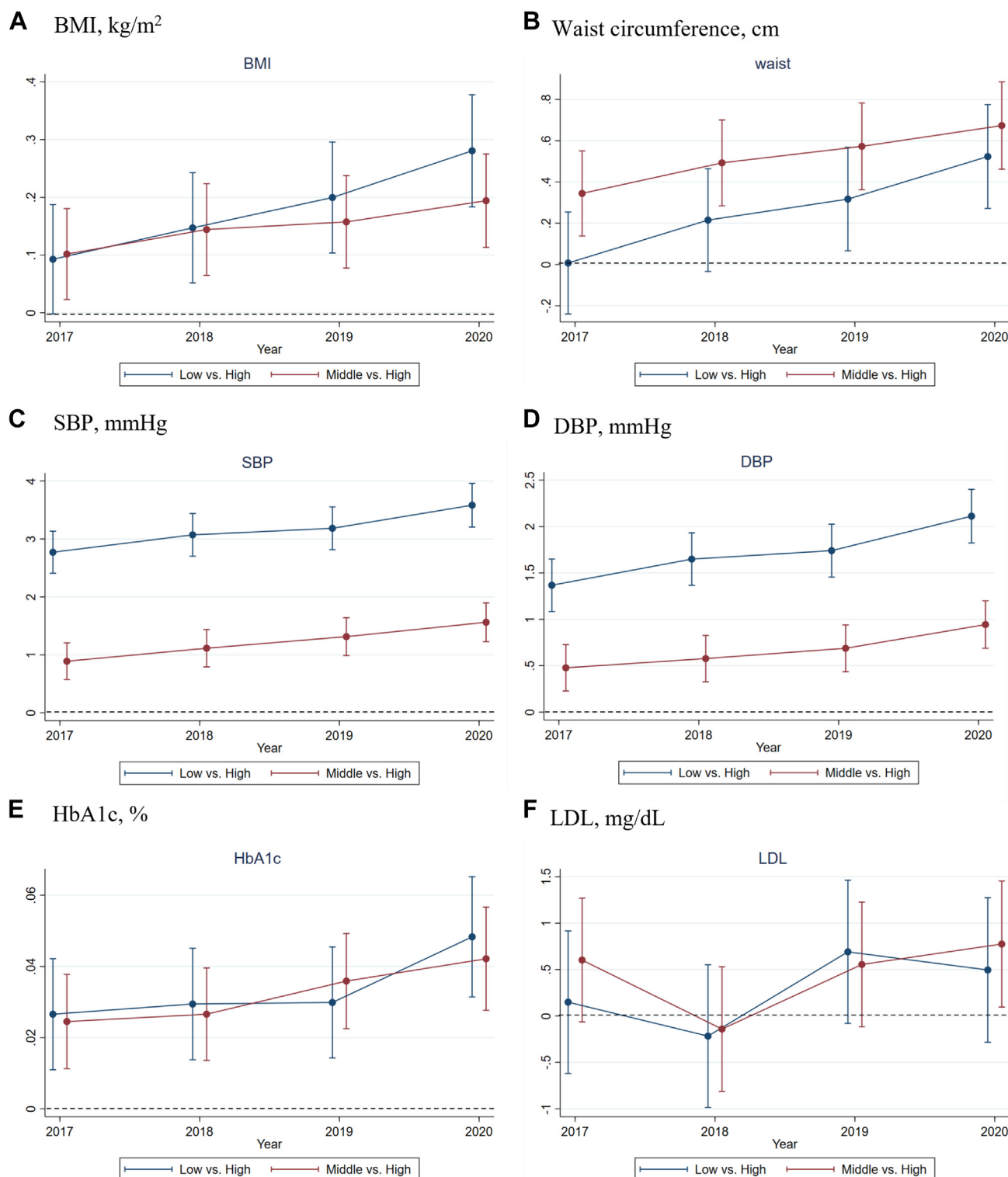
years among young individuals. Evidence focusing on young working-age adults is important because they have multilevel complex risks of CVD including genetic factors, gender, social relationship, neighborhood factors, adverse childhood experiences, and psychological factors.<sup>27</sup> Previous studies have shown the association between low socioeconomic status and risk behaviors of CVD, such as exposure to passive and active smoking, physical inactivity, sedentary behavior, and poor sleep quality and quantity among young adults.<sup>28</sup> Furthermore, the presence of CVD risk factors at this life stage would lead to health consequences later in life<sup>5</sup> and substantial economic burden through decreased productivity<sup>29</sup>; eg, the increase in production costs and employee absence or disability among people with CVD or related clinical procedures.<sup>30,31</sup> In this context, our findings of the increased income disparity of CVD risk factors suggest the need for further aggressive tailored intervention focusing on young working-age people with low-income levels to prevent future CVD events and loss of social productivity.

Our findings are in line with a previous report suggesting the presence of societal factors beyond the healthcare system that contribute to health outcomes,<sup>32</sup> which should be acknowledged by clinicians, particularly those treating patients with low socioeconomic status (even in a country with universal healthcare

coverage system). Moreover, there are some potential strategies to ease the observed health disparities although their feasibility and effectiveness are still unclear. For example, behavioral counseling has been shown to be effective in reducing cholesterol levels, blood pressure, and incidence of diabetes mellitus.<sup>33</sup> Internet-based smoking cessation programs were also shown to be effective in the low-income population according to a previous study.<sup>34</sup> Furthermore, because individuals with low-income levels are less likely to have access to safe facilities of exercise and infrastructure,<sup>35</sup> programs and/or policies to increase their leisure-time physical activity levels would be a promising strategy to improve their cardiovascular risks.<sup>36</sup> Reducing the costs of healthy foods is another important step to help individuals at low-income levels to sustain healthy diet behavior.<sup>37</sup>

Increasing trends were continuously observed during the study period, and we did not find a specific acceleration in the income disparity of CVD risk factors during 2020 (ie, during the COVID-19 pandemic). Because it is plausible that behavioral change and psychological stress due to the pandemic may increase the cardiovascular health burden,<sup>9,38</sup> additional nationwide follow-up of CVD risk factors by socioeconomic factors is strongly recommended. Moreover, given the increased risks of unfavorable lifestyles, chronic diseases, CVD, and death among the





**Fig. 2.** Adjusted trends in the difference in the measurements of cardiovascular risk factors from 2017 to 2020 across income tertiles in 2017 among men. The model adjusted for age, smoking, alcohol intake, and number of household members, along with regional fixed effects and calculated clustered standard error to consider correlation within individuals. We also included the indicator variable of the year (2017, 2018, 2019, and 2020) and the interaction terms between the income groups and the year indicator variable to assess the statistical trends over time.

high-occupational classes (eg, managers and professionals) compared to other occupational classes particularly among men in Japan,<sup>39–42</sup> investigation of the income disparities in cardiovascular health by individuals' occupation types and classes during this unprecedented time should also be the subject of future research.

### Limitations

Although our study has the strength of using nationwide longitudinal data with valid information on individual income levels, it has several limitations. First, given the lack of information on other

socioeconomic indicators, such as education levels and marital status, our study might have suffered from unmeasured confounding. Second, each of the CVD risk factors was measured at one time per year during the annual health screening; therefore, there might be measurement error in these factors. However, such information bias is expected to occur at random; thus, it should not be related to an individual's income level (ie, nondifferential misclassification of disease outcomes). Third, information on covariates, such as health behavior and comorbidities, might have been misclassified due to self-reporting. Fourth, because we used the database of the Health Insurance Association for Architecture and Civil Engineering companies in Japan, the majority of the study participants were men, and we did not have enough statistical power for some analyses among women. Finally, our results may not be generalizable or transportable to other populations, particularly because of the variety of healthcare systems across countries.

## Conclusion

Among the young working-age population in Japan where insurance is comprehensively covered, there have been social disparities in CVD risk factors according to income levels. The disparities, particularly in the prevalence of hypertension, increased between 2017 and 2020. Given both the health and economic burden of these CVD risk factors among the young working-age population, careful and close monitoring of the increasing social disparities is needed to develop effective strategies to achieve the best attainable cardiovascular health at this life stage.

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## Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author

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## Author Contributions

K.I. and S.F. had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. K.I. and S.F. were responsible for concept and design. K.I., N.K., K.S., and S.F. acquired, analyzed and interpreted data. K.I., N.K., K.S., and S.F. drafted the manuscript. K.I., N.K., K.S., and S.F. critically revised the manuscript for important intellectual content. K.I. and S.F. statistically analyzed the data.

## Disclosures

The authors have no multiplicity of interest to disclose.

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