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Original Investigation

Smoking Cessation, Weight Gain, and the Trajectory of Estimated Risk of Coronary Heart Disease: 8-Year Follow-up From a Prospective Cohort Study

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Abstract

Introduction: The effect of weight gain following smoking cessation on cardiovascular risks is unclear. We aimed to prospectively investigate the association of weight gain following smoking cessation with the trajectory of estimated risks of coronary heart disease (CHD).

Methods: In a cohort of 18 562 Japanese male employees aged 30–64 years and initially free of cardiovascular diseases, participants were exclusively grouped into sustained smokers, quitters with weight gain (body weight increase ≥5%), quitters without weight gain (body weight increase <5% or weight loss), and never smokers. Global 10-year CHD risk was annually estimated by using a well-validated prediction model for the Japanese population. Linear mixed models and piecewise linear mixed models were used to compare changes in the estimated 10-year CHD risk by smoking status and weight change following smoking cessation.

Results: During a maximum of 8-year follow-up, both quitters with and without weight gain had a substantially decreased level of estimated 10-year CHD risk after quitting smoking, compared with sustained smokers (all *p*s for mean differences < .001). The estimated 10-year CHD risk within the

first year after cessation decreased more rapidly in quitters without weight gain than in quitters with weight gain (change rate [95% confidence interval, CI] –0.90 [–1.04 to –0.75] vs. –0.40 [–0.60 to –0.19] % per year, $p < .0001$). Thereafter, the estimated 10-year CHD risk in both groups increased at similar rates (change rate [95% CI] –0.07 [–0.21 to 0.07] vs. 0.11 [–0.09 to 0.30] % per year, $p = .16$, from year 1 to year 2; and 0.10 [0.05 to 0.15] vs. 0.11 [0.04 to 0.18] % per year, $p = .80$, from year 2 to year 8).

Conclusions: In this population of middle-aged, Japanese male workers, smoking cessation greatly reduces the estimated 10-year risk of CHD. However, weight gain weakens the beneficial effect of quitting smoking in a temporary and limited fashion.

Implications: To the best of our knowledge, this study is the first to examine the effect of weight gain following smoking cessation on the trajectory of the absolute risk of CHD. Our data imply that the benefits of cessation for reducing the absolute risk of CHD outweigh the potential risk increase due to weight gain, and suggest that in order to maximize the beneficial effects of quitting smoking, interventions to control post-cessation weight gain might be warranted.

Introduction

Smoking cessation reduces the risks of cardiovascular diseases (CVD) and increases life expectancy[1,2]; however, quitting smoking is often accompanied by weight gain.[3] The weight gain is likely owing to increased appetite and decreased energy expenditure after nicotine absence[4,5] and has been a concern of smokers for not trying to quit or for relapsing after an attempt to quit.[6] It has been reported that weight gain following smoking cessation is associated with deteriorating changes in several CVD risk factors including blood pressure (BP), blood glucose, and lipids.[7–11] This has raised questions regarding whether the affiliated weight gain weakens the global CVD benefits of smoking cessation.

To date, few studies have investigated this association and the findings from these studies are inconsistent.[12–14] A study of postmenopausal American women showed that the magnitude of coronary heart disease (CHD) risk reduction after smoking cessation was weakened when weight gain occurred.[12] However, in other studies of middle-aged American men and women[13] and middle-aged Korean men,[14] weight gain did not have such an effect. In addition to these inconsistencies, some limitations associated with the previous studies remain to be addressed.[12–14] First, prior studies[12–14] solely ascertained smoking cessation at baseline; those who relapsed to smoking were not excluded from those who were indicated as having quit, resulting in potential bias in results due to misclassification. This is extremely important as a meta-analysis showed that those who quit smoking had a 10% annual incidence of relapse after 1-year abstinence.[15] Second, risk reductions for CVD in prior studies[12–14] were estimated based on a relative risk averaged over the entire follow-up. Thus, it is unclear whether the magnitude of risk reduction by post-cessation weight gain changes over time. Investigating the trajectory of individuals' absolute risk of CVD after cessation may improve our understanding of the effect of weight gain, as the estimate can present individual's CVD risk at any given timepoint and enable comparisons over time with repeat assessments.[16,17] One study in Japan found a 24% reduction in the estimated risk of CHD after smoking cessation[18]; but that study did not examine the effect of weight gain on the magnitude of the risk reduction.

In Japan, although the smoking prevalence among men has been decreasing due in part to tobacco control laws and policies, it is still much higher than that among women (28% in men vs. 9% in women in 2017).[19,20] Thus, smoking cessation research remains important, particularly among men. In this study, with repeated assessments of smoking behavior, we aimed to investigate the association of weight gain following smoking cessation with the changes in the estimated 10-year risk of CHD. We compared the trajectory of the estimated 10-year CHD risk, according to weight changes after smoking cessation in a large cohort of middle-aged, working Japanese men.

Methods

Study Design

We used data from the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study, which is an ongoing multicenter longitudinal study among workers at 12 companies across various industries.[21,22] The workers underwent annual health checkups, comprising anthropometric measurements, physical examinations, laboratory examinations, and a self-administrated questionnaire about medical history and health-related lifestyle factors. Almost all workers underwent the annual health checkup, as it is compulsory for all employees according to the Industrial Safety and Health Act in Japan. As of May 2017, 11 participating companies provided health checkup data between January 2008 and December 2016 or between April 2008 and March 2017. Data from the earliest health checkup (the 2008 dataset) were considered as the baseline of this cohort; however, if the 2008 dataset had a large amount of missing data, the data from the 2009 or 2010 (one company each) health checkup were used as the baseline.

The objectives and procedures of the J-ECOH study were explained using posters placed at each company prior to data collection. Although participants were not required to provide verbal or written informed consent, they could refuse to participate and withdraw from participation at any time. This procedure conforms to the Japan Ethical Guideline for Epidemiological Research, which suggests that informed consent from each participant is not necessarily required for observational studies using existing data. The research protocol including the consent procedure was approved by the ethics committee of the National Center for Global Health and Medicine, Japan.

Study Participants

Of 95 018 participants from the 11 companies who underwent the baseline health checkup, we excluded 4983 participants from two companies due to a lack of information on past smoking. Of the remaining 90 035 participants, 67 870 men aged 30–64 years were eligible for this study (Supplementary Figure 1). We did not

include women because in the final sample too few (24 of 253 female smokers) quit and remained abstinent during the study period. At baseline, we excluded participants with a history of CVD (stroke or ischemic heart diseases) or cancer, with missing data on smoking status or body weight, and who were former smokers. At follow-up, we excluded participants who did not attend any subsequent health checkups or those having no data on smoking status during the entire follow-up or no data on post-cessation weight change. To minimize misclassification of smoking status, we excluded those who started smoking or relapsed after quitting during the entire follow-up period, and those who reported logically invalid changes in smoking status (ie, current smoker on one occasion and never smoker later). Of the remaining 34 189 participants, 18 562 participants (8560 never smokers, 1233 quitters, and 8769 sustained smokers) who had complete data to estimate 10-year CHD risk at baseline comprised the final sample of included participants.

General Health Examination and Laboratory Measurements

Smoking status (never, former, or current) was assessed using the self-administrated questionnaire. Body weight and height were measured in light clothes and without shoes. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. BP was measured in a sitting position with an automatic sphygmomanometer. Plasma blood glucose was measured using an enzymatic or a glucose oxidase preoxidative electrode method. Blood lipids were measured enzymatically including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides. Glycated hemoglobin (HbA1c) was measured using a latex agglutination immunoassay method, the high-performance liquid chromatography method, or the enzymatic method. Serum creatine (Cre) was measured enzymatically.

Smoking Status and Weight Change

Smoking status (never, former, or current) was measured by a self-administered questionnaire. We defined never smokers as being never smokers for the entire study and sustained smokers as being current smokers for the entire study. We identified quitters as current smokers who became former smokers later and remained abstinent for the rest of the follow-up. We used a forward timeline scale, setting the year prior to reporting having quit smoking as year 0 (the baseline year), the year of reporting having quit smoking as year 1, years after reporting having quit smoking as years 2–8. Thus, the exact time of smoking cessation was between years 0 and 1. The timeline for the research design is illustrated in Supplementary Figure 2.

Weight change was defined as weight at year 2 minus weight at year 0, reflecting 2-year weight change concomitant with or shortly following smoking cessation, as a previous Korean study did for defining weight gain after smoking cessation.[14] The 2-year time window was also based on our observation that the average weight of quitters increased from year 0 to year 2 but changed minimally thereafter (Supplementary Figure 3). Percent weight change was calculated as post-cessation weight change divided by weight at year 0. We defined an increase of at least 5% as having weight gain whereas less than 5% (including weight loss) was defined as having no weight gain, as prior studies have associated the cutoff point of at least 5% with adverse outcomes.[23,24] Quitters were categorized into two groups: quitters with and without weight gain.

Estimated 10-Year CHD Risks

We estimated the 10-year CHD risk using a prediction model for the Japanese population, also known as the LDL Suita score,[25] as recommended by the Japan Atherosclerosis Society.[26] The risk factors for calculating the Suita score include age, sex, smoking status, diabetes, systolic and diastolic BP, LDL-C, high-density lipoprotein cholesterol, and chronic kidney disease. We defined diabetes as HbA1c at least 6.5%, fasting plasma glucose at least 126 mg/dL, random plasma glucose at least 200 mg/dL, or currently under medical treatment for diabetes, according to the American Diabetes Association criteria.[27] As originally developed,[25] the chronic kidney disease stage was defined based on the estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2), which was calculated from the serum Cre level using an equation that was modified using Japanese coefficients: $eGFR = 0.881 \times 186 \times age^{-0.203} \times Cre^{-1.154}$ for males.

Covariates

Covariates included age, work-site, and BMI at year 0. In one major company, information on the following variables at year 0 were also collected via a self-administrated questionnaire: alcohol consumption, leisure-time physical activity, sleep duration, and family history of ischemic heart diseases (n = 9940). These variables were further adjusted for in a sensitivity analysis.

Statistical Analyses

We summarized means and frequencies of baseline characteristics based on smoking category. We used Pearson chi-square tests and analysis of variance tests to compare the baseline characteristics.

Our primary analyses for evaluating changes in the estimated 10-year CHD risk across the follow-up period were composed of two stages. First, we calculated the least square means of estimated 10-year CHD risks of the four groups from year 0 to year 8, using a linear mixed model for repeated measures. In the linear mixed model, we compared the mean levels of quitters with and quitters without weight gain with those of sustained smokers. The linear mixed model accommodates within-subject correlation and unequal numbers of observations per subject.[28] Interaction terms for time based on smoking group were included. Second, we evaluated the annual change rate in the estimated 10-year CHD risks based on smoking category using a piecewise linear mixed model. This model allows for comparisons in the annual change rate between the groups.[28] With the sample size in this study, we had sufficient power to provide reliable estimates. We divided the entire follow-up period into three time segments based on the timing of changes observed from the general shape of the mean levels of the estimated 10-year CHD risks: (1) from year 0 to year 1, representing 1 year before smoking cessation; (2) from year 1 to year 2, representing 1 year after smoking cessation; and (3) after year 2, representing more than 1 year after smoking cessation. Furthermore, we statistically tested the nonlinear trend of changes in the estimated 10-year CHD risks by including time squared and an interaction term of time squared with smoking group in the linear mixed model. We confirmed a possible quadratic trend ($p < .001$). We modeled three time segments in the random effect.[29] We assumed an unstructured covariance matrix and chose the restricted maximum likelihood method for the covariance parameter estimation and Kenward–Roger correction[30] for the denominator degrees of freedom. Our choice of these methods was supported by the comparisons of model fit statistics, the Akaike information criterion and the Bayesian information criterion. All models were

adjusted for baseline age (continuous, years), work-site, and baseline BMI (continuous, kg/m^2). To improve the interpretability of the parameter estimates, we centered baseline age and BMI at the mean of each smoking group.

To further illustrate the effects of weight change, we computed and plotted the predicted values of the estimated 10-year CHD risk over time (regression line) according to different levels of weight change among quitters. We fit a piecewise linear mixed model that included a smoking category with three groups (never smokers, quitters, and sustained smokers) and weight change as a continuous variable, so as to include a function of different levels of weight change.[29] To that end, we selected weight change in quitters corresponding to the 10th percentile (weight change = −2.0 kg), the 50th percentile (weight change = 2.0 kg), and the 90th percentile (weight change = 6.2 kg). The weight changes in sustained smokers and never smokers corresponding to the 50th percentile (weight change = 0.1 kg and 0.2 kg, respectively) were also chosen as references. This model was also adjusted for baseline age (centered at the mean), work-site, and baseline BMI (centered at the mean).

We also examined the longitudinal changes for the following CVD risk factors by constructing separate piecewise linear mixed models: systolic BP, diastolic BP, blood glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglycerides. We selected participants who did not take antihypertensive medication for analyses of BP, participants who did not receive medical treatment for diabetes for analyses of blood glucose, and participants who did not take lipid-lowering medication for analyses of lipids and lipoproteins.

We performed two sensitivity analyses: (1) using multiple imputation and combined the parameter estimates from each imputed data set (k = 15)[31] to evaluate the potential impact of missing observations (19%); (2) further adjusting for alcohol consumption (<23 or ≥23 g ethanol/d), sleep duration (<6, 6 to <7, or ≥7 h/d), leisure-time physical activity (<150 or ≥150 min/wk), and family history of ischemic heart disease (yes or no). All statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC).

Results

The mean (SD) observation period was 6 (2) years. The median 2-year weight change of quitters was 2 kg (interquartile range [IQR], 0.1 to 4.2). A total of 419 (34%) quitters had a weight gain at least 5% (a median increase of 5.1 kg [IQR, 4.1 to 6.4]). Baseline characteristics based on the smoking category are summarized in Table 1.

Figure 1 shows the adjusted mean levels of the 10-year CHD risk estimated at different timepoints. The 10-year CHD risk estimated at baseline (year 0) did not statistically differ among the sustained smokers, quitters with weight gain, and quitters without weight gain. From year 1 to 8, both quitters with and without weight gain had a substantially lower level of estimated 10-year CHD risk, compared with sustained smokers. The adjusted mean differences (vs. sustained smokers) were the following: −0.73% (95% confidence interval [95% CI], −1.2% to −0.2%) at year 1, −0.69% (95% CI, −1.2% to −0.2%) at year 2, and −1.0% (95% CI, −2.2 to 0.2) at year 8 for quitters with weight gain; −0.9% (95% CI, −1.2% to −0.5%) at year 1, −1.1% (95% CI, −1.5% to −0.7%) at year 2, and −1.6% (95% CI, −2.3% to −0.9%) at year 8 for quitters without weight gain (all ps for mean differences < .001).

Table 2 shows the annual change rate of the estimated 10-year CHD risk across the entire follow-up period. The estimated 10-year CHD risk from year 0 to 1 decreased more rapidly in quitters without weight gain than that in quitters with weight gain (change rate [95% CI] −0.90 [−1.04 to −0.75] vs. −0.40 [−0.60 to −0.19] % per year, p < .0001). From year 1 to 2, there was a downward trend among quitters without weight gain and an upward trend among quitters with weight gain, but the difference did not reach statistical significance (change rate [95% CI] −0.07 [−0.21 to 0.07] vs. 0.11 [−0.09 to 0.30] % per year, p = .16). From year 2 to 8, the estimated 10-year CHD risk in both groups increased at similar rates (the change rate [95% CI]: 0.10 [0.05 to 0.15] vs. 0.11 [0.04 to 0.18] % per year, p = .80).

Figure 2 illustrates the regression lines for the estimated 10-year CHD risk over time among those selected quitters who had weight

Table 1. Baseline Characteristics of the Study Sample by Smoking Categories, the Japan Epidemiology Collaboration on Occupational Health Study, 2008–2016

	Sustained smokers (n = 8769)	Quitters with weight gain[a] (n = 419)	Quitters without weight gain[b] (n = 814)	Never smokers (n = 8560)	p[c]
Age (mean ± SD, years)	44.8 ± 8.2	45.0 ± 8.1	45.7 ± 8.0	44.3 ± 8.2	<.001
BMI (kg/m^2)	23.8 ± 3.5	23.0 ± 3.0	23.9 ± 3.0	23.6 ± 3.2	<.001
Weight (kg)	69.4 ± 11.5	66.1 ± 9.0	69.6 ± 9.9	68.7 ± 10.6	<.001
Weight change[d] (kg)					<.001
Mean (SD) [95% CI]	0.06 (3.2) [0.0 to 0.1]	5.6 (2.1) [5.4 to 5.8]	0.1 (2.8) [−0.04 to 0.3]	0.06 (3.2) [0.0 to 0.1]	
Median (IQR)	0.1 (−1.5 to 1.8)	5.1 (4.1 to 6.4)	0.7 (−0.8 to 2.0)	0.2 (−0.2 to 1.8)	
Percent weight change (% [95% CI])	0.2 [0.1 to 0.3]	8.5 [8.2 to 8.9]	0.3 [0.01 to 0.5]	0.2 [0.1 to 0.3]	<.001
Alcohol consumption (>23 g ethanol/d, %)[e]	28.9	30.1	33.0	13.7	<.001
Leisure-time physical activity (≥150 min/wk, %)[e]	11.5	11.0	16.0	14.2	<.001
Sleep time (<6 h/d, %)[e]	50.4	47.8	48.6	55.7	<.001
Family history of ischemic heart diseases (yes, %)[e]	8.6	8.5	11.8	8.3	.10

BMI = body mass index; CI = confidence interval; IQR = interquartile range.

[a]Percent weight change ≥5% was defined as weight gain.

[b]Percent weight change <5% was defined as having no weight gain.

[c]Calculated by using the Pearson chi-square test for categorical variables and an analysis of variance test for continuous variables.

[d]Calculated as the weight difference between the year prior to reporting having quit smoking and 1 year after reporting having quit smoking, reflecting 2-year weight change concomitant with or shortly following smoking cessation.

[e]Data available for 10 060 participants.

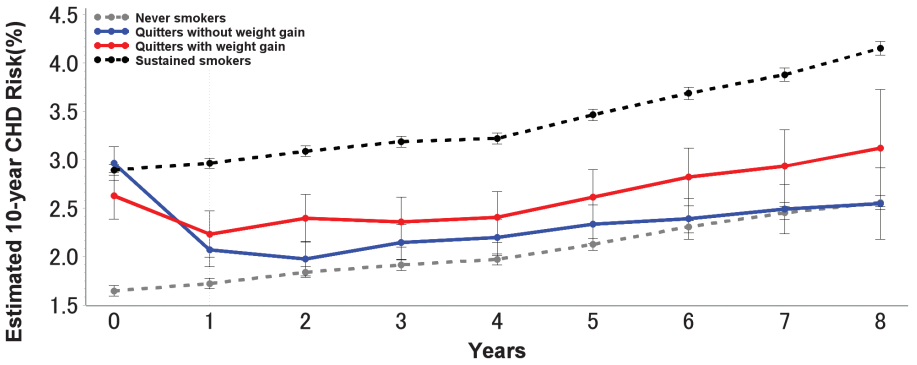

Figure 1. Adjusted means of estimated 10-year risk of coronary heart disease (CHD) across the follow-up period, the Japan Epidemiology Collaboration on Occupational Health Study, 2008–2016. The least square means and 95% confidence intervals were estimated using the linear mixed model, adjusted for age (centered at the group mean), work-site, and baseline body mass index (centered at the group mean). The time of smoking cessation was between year 0 and year 1.

Table 2. Annual Change Rates of Estimated 10-Year CHD Risk (%) Across the Follow-up Period by Smoking Categories, the Japan Epidemiology Collaboration on Occupational Health Study, 2008–2016[a]

	Annual change rate (95% CI)		
	Years 0–1	Years 1–2	Years 2–8
Sustained smokers	0.07 (0.03 to 0.12)	0.04 (–0.003 to 0.09)	0.17 (0.16 to 0.18)
Quitters with weight gain[b]	–0.40 (–0.60 to -0.19)	0.11 (–0.09 to 0.30)	0.11 (0.04 to 0.18)
Quitters without weight gain[c]	–0.90 (–1.04 to -0.75)	–0.07 (–0.21 to 0.07)	0.10 (0.05 to 0.15)
Never smokers	0.06 (0.02 to 0.11)	0.09 (0.05 to 0.14)	0.12 (0.11 to 0.13)
p for the difference (quitters with weight gain vs. quitters without with gain)	<.0001	.16	.80

CHD = coronary heart disease; CI = confidence interval.

[a]The time of smoking cessation was between year 0 and year 1. All parameter values were adjusted for age (centered at the group mean), work-site, and baseline body mass index (centered at the group mean).

[b]Percent weight change ≥5% was defined as weight gain.

[c]Percent weight change <5% was defined as having no weight gain.

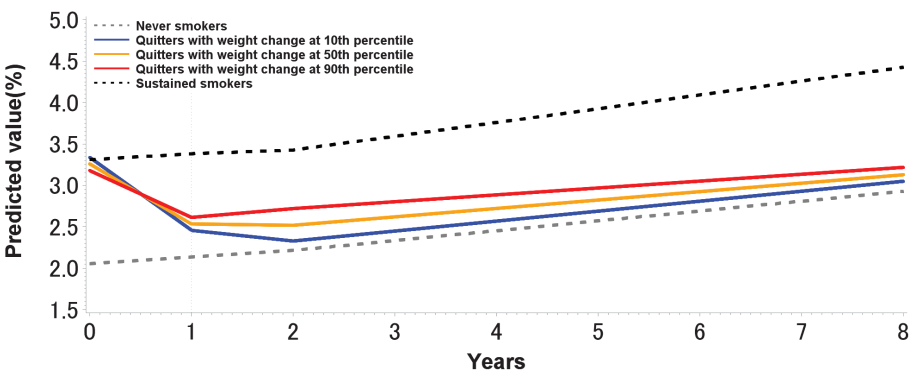

Figure 2. Predicted value of estimated 10-year risk of coronary heart disease (CHD) across the follow-up period as a function of different levels of weight change, the Japan Epidemiology Collaboration on Occupational Health Study, 2008–2016. The parameter values were estimated using the piecewise linear mixed-effects model. Weight change in quitters corresponding to the 10th percentile (weight change = –2.0 kg), the 50th percentile (weight change = 2 kg), and the 90th percentile (weight change = 6.2 kg) were selected to plot the predicted values of estimated 10-year risks of CHD, after controlled for age (centered at the group mean), work-site, and baseline body mass index (centered at the group mean). Weight change in sustained smokers and never smokers corresponding to the 50th percentile (weight change = 0.1 kg and 0.2 kg, respectively) were chosen as the reference. The time of smoking cessation was between year 0 and year 1.

changes noted at the 10th, 50th, 90th percentile. The predicted value of the estimated 10-year CHD risk among those selected quitters at various timepoints over the entire 8-year follow-up was continuously lower than that among sustained smokers.

In the analyses of longitudinal changes in individual CVD risk factors (Supplementary Figure 4 and Supplementary Table 3), from year 0 to year 1, quitters with weight gain experienced a more pronounced increase in systolic and diastolic BP, blood glucose, total cholesterol, LDL-C, and triglycerides, whereas a smaller increase in high-density lipoprotein cholesterol, as compared with quitters without weight gain. Similar differences persisted between the two groups from year 1 and year 2; but not thereafter.

In sensitivity analyses, the results did not materially change when we used multiple imputation to address the missing values for the estimated 10-year CHD risk (Supplementary Table 1). In addition, further adjustments for alcohol consumption, sleep duration, leisure-time physical activity, and family history of ischemic heart diseases did not significantly alter the estimates (Supplementary Table 2).

Discussion

In this large cohort of middle-aged Japanese men, we observed a substantial reduction in the estimated 10-year CHD risk after smoking cessation, despite weight gain. The change in the estimated 10-year CHD risk within the first year after smoking cessation, but not thereafter, was more pronounced in quitters without weight gain than that in quitters with weight gain. These findings suggest that weight gain attenuated the benefits of smoking cessation in reducing the estimated 10-year CHD risk, in a temporal and limited manner. To the best of our knowledge, this study is the first to examine the effect of weight gain following smoking cessation on the change of the absolute risk of CHD over time.

Our observations cannot be directly compared with findings from previous studies which investigated the relative risk reduction of incident CVD[12–14] and CVD mortality.[32] In the Women's Health Initiative study, a weight gain of 5 kg or more after smoking cessation attenuated the association between smoking cessation and CHD risk.[12] That study included only postmenopausal women; the findings, therefore, could not be generalized to men.[12] In contrast, two studies of middle-aged American men and women found that the risk reduction for CHD[13] and CVD[32] mortality after smoking cessation was not mitigated among quitters who gain 5–10 kg or 10 kg or more. In Asian populations, one study of 1995 Japanese male workers found that quitters had a 24% decreased estimated risk of CHD during a 4-year follow-up despite an average of 2-kg weight gain,[18] but the investigators did not examine whether the magnitude of risk reduction differed by the amount of weight change. One study of middle-aged Korean men[14] showed that quitters who had stable body weight or a weight gain of 2 kg or more had a statistically lower CHD risk, compared with sustained smokers. However, that study was not able to determine whether the results would differ if Asian smokers gained more weight.[33] In our study of approximately 20 000 middle-aged Japanese male workers, first, we observed that the absolute 10-year CHD risk of those who quit smoking estimated at various timepoints over an 8-year follow-up was continuously lower than that among sustained smokers, even when a relatively large weight gain (6.2 kg, at the 90th percentile of weight change) occurred. These findings suggest that the effect of weight gain did not outweigh the benefits of quitting smoking for reducing the estimated 10-year CHD risk. Second, we observed that the rate of decline in the estimated 10-year CHD risk among those who quit smoking with weight gain was less than half of that among those who quit smoking without weight gain (–0.4% vs. –0.9% per year, $p < .0001$) within the first year after cessation. Thereafter, the estimated 10-year risk in these two groups slowly rose at approximately similar rates, indicating that weight gain did not persistently increase the estimated 10-year CHD risk. Taken together, in this study among a middle-aged Japanese working population, our results demonstrate that quitting smoking was beneficial for reducing the estimated 10-year CHD risk; subsequent weight gain temporarily attenuated the beneficial effects of cessation. Our data imply that the benefits of cessation in reducing the absolute risk of CHD outweigh the potential risk due to weight gain. Finally, they suggest that in order to maximize the beneficial effects of quitting, interventions to control post-cessation weight gain might be warranted.

We also observed more harmful changes in some CVD risk factors in quitters with weight gain than in quitters without weight gain from year 1 to year 2. However, the changes in those risk factors did not lead to a significant difference in the estimated CHD risk between the two groups. Nevertheless, these findings indicate the importance of weight control following smoking cessation to improve those CVD risk factors.

The strengths of our study include the large sample size, up to 8 years of follow-up, the reliable repeated measures of CHD risk factors and body weight from health examinations, and minimized misclassification of smoking status, which accounts for quitting or relapsing to smoking during the entire follow-up. There are also several important limitations to note. First, smoking exposure was self-reported, not biochemically verified. However, the annual repeated measure, exclusion of those who relapsed from those who quit smoking during the entire follow-up and invalid changes in smoking status may have assured the reliability of this measure. Second, there was a lack of data in approximately two-thirds of the final sample on lifestyle factors such as alcohol consumption, sleep duration, leisure-time physical activity, and self-reported family history of angina and myocardial infarction. However, our sensitivity analysis with further adjustments for those factors among a subgroup of participants confirmed our results. Third, although mixed model methodology does not require complete data of repeated measures, we could not rule out the possibility that missing observations could have distorted our results. After we imputed missing values for the estimated 10-year CHD risk using multiple imputation, our results did not significantly alter. Fourth, because this study only included men, our findings cannot be generalized to women. Females have been shown to have greater weight gain after nicotine cessation compared with males in randomized controlled trials of humans[34,35] and rats,[36,37] although a meta-analysis of 35 cohort studies did not reveal a statistically significant sex difference.[38] There is a chance that weight gain after smoking cessation might be associated with a greater adverse impact on CVD risks in women than in men.

In conclusion, the present large prospective study of middle-aged Japanese men demonstrated that smoking cessation greatly reduces the estimated 10-year risk of CHD, and that weight gain weakens the beneficial effect of quitting in a temporary and limited manner. Our findings not only strongly confirm the CHD benefits of smoking cessation in male Japanese workers, but also support the inclusion of weight control interventions as part of smoking cessation programs to maximize the CHD benefits.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

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