

# Recurrent Pregnancy Loss and Cardiovascular Disease Mortality in Japanese Women: A Population-Based, Prospective Cohort Study

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*Background:* This study aimed to examine the association between recurrent pregnancy loss and the risk of cardiovascular disease mortality. *Methods:* We identified 54,652 women who were pregnant during the Japan Collaborative Cohort Study. These women were 40-79 years at the date of cohort entry between 1988 and 1990. Participants received municipal health screening examinations and completed self-administered questionnaires. The cause of death was confirmed by annual or biannual follow-up surveys for a median of 18 years. The exposure was the number of pregnancy loss. The outcome was mortality from total cardiovascular disease and its subtypes according to the International Classification of Diseases, 10th Revision. Adjustment variables included age, number of deliveries, education, body mass index, physical activity, smoking status, and drinking status. Kaplan-Meier survival curves were used to estimate the cumulative mortality. *Results:* The number of pregnancy loss tended to be inversely associated with the risk of mortality from total stroke, intracerebral hemorrhage, and total cardiovascular disease. The multivariable hazard ratio of total cardiovascular disease for  $\geq 2$  pregnancy losses versus no pregnancy loss was .84 (95% confidence interval, .74-0.95). A 2-fold excess risk of mortality from ischemic stroke associated with  $\geq 2$  pregnancy losses was observed in women aged 40-59 years, with a multivariable hazard ratio of 2.19 (95% confidence interval, 1.06-4.49), but not in older women. *Conclusions:* Recurrent

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Received June 19, 2016; revision received December 16, 2016; accepted December 23, 2016.

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Grant support: This research was supported by a grant-in-aid from the Health and Labor Sciences research grants of the Ministry of Health, Labour and Welfare, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular Disease and Life-Related Disease: H18-Junkankitou[Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular Disease and Life-Related Disease: H19-Junkankitou [Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular and Lifestyle Related Diseases: H20-Junkankitou [Seishuu]-Ippan-013; Comprehensive Research on Cardiovascular and Lifestyle Related Diseases: H23-Junkankitou [Seishuu]-Ippan-005, H25-Junkankitou [Seishuu]-Ippan-003, and an Intramural Research Fund [22-4-5] for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; and Comprehensive Research on Cardiovascular and Lifestyle Related Diseases: H26-Junkankitou [Seisaku]-Ippan-001). This research was also supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), and Grants-in-Aid for Scientific Research on Priority Areas of Cancer, as well as Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Monbu-Kagaku-sho) (Nos 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, and 26293138).

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1052-3057/\$ - see front matter

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<http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.12.018>

pregnancy loss tends to be associated with a lower risk of mortality from cardiovascular disease at 40-79 years. Younger women have an excess risk of ischemic stroke mortality associated with recurrent pregnancy loss. **Key Words:** Abortion—miscarriage—stillbirth—cardiovascular disease—cerebral infarction.  
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## Introduction

Pregnancy loss is the most common pregnancy-related complication and represents a significant clinical burden. A history of pregnancy loss may be useful for making a clinical decision to investigate the presence of autoimmune disease or congenital coagulation disorders. We hypothesize that hematological disorders or abnormal vasoconstriction may contribute to the risk of cardiovascular disease (CVD) mortality among women with recurrent pregnancy loss.

The American Heart Association guidelines that were updated in 2011 state that cardiovascular and metabolic stress during pregnancy (e.g., preeclampsia, gestational diabetes) should be regarded as an indicator of the risk of CVD, including ischemic stroke and coronary heart disease, in women.<sup>1</sup> Additionally, a careful and detailed history of complications in pregnancy should be taken by a primary care physician or cardiologist.<sup>1</sup> However, epidemiological evidence for the risk of complications in pregnancy on long-term CVD is limited in Chinese<sup>2</sup> and Japanese populations.<sup>3</sup> A Chinese cohort study showed that women with multiple stillbirths or miscarriages did not have an increased risk of ischemic heart disease and ischemic stroke mortality.<sup>2</sup> A Japanese cross-sectional study with a much smaller number of subjects, 2733 women aged 35-79 years, reported that single miscarriage and recurrent spontaneous abortion were not associated with a history of ischemic heart disease and stroke.<sup>3</sup>

Congenital hematological or vascular wall disorders may contribute to the risk of ischemic CVD mortality in younger adults.<sup>4,7</sup> A Danish population-based cohort study showed that the risks of ischemic stroke and myocardial infarction associated with each additional miscarriage were larger in women aged <35 years than in older women.<sup>8</sup>

Because of the limited available evidence, we examined the association between recurrent pregnancy loss and risk of mortality from total stroke, stroke subtypes, coronary heart disease, and total CVD using data from a large Japanese cohort. In this study, we also analyzed the data based on the age subgroups of 40-59 years and 60-79 years at baseline.

## Materials and Methods

### *Study Design*

All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation, the Ethics Boards of the Nagoya University Graduate School and Osaka University Graduate School of Medicine, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The Japan Collaborative Cohort Study was described previously.<sup>9</sup> A total of 110,585 people (64,190 women) aged 40-79 years from 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires from 1988 to 1990.<sup>9</sup> Participants were followed up until 2009 in 35 of 45 areas. Follow-up was terminated in 1999 in 4 areas, in 2003 in 4 areas, and in 2008 in 2 areas (median follow-up: 18 years).<sup>9</sup>

Participants were censored at death or when they moved from the surveyed community. The date and cause of death or the date of movement away from the study area was annually or biannually confirmed using population registers until the end of the study. These population data were shared with the public health center and local governmental office.<sup>9</sup>

A total of 1,025,703 person-years were followed up for women. Mortality with an identified cause was coded according to the 10th revision of the International Classification of Diseases,<sup>9</sup> including total stroke (I60-I69), ischemic stroke (I63), hemorrhagic stroke (I60 and I61), intracerebral hemorrhage (I61), subarachnoid hemorrhage (I60), coronary heart disease (I20-I25), and total CVD (I01-I99). Follow-up surveys were approved by the Director General of the Prime Minister's Office and the Ministry of Health, Labour and Welfare, Japan. Registration of death was reported as required under the Family Registration Law of Japan.<sup>9</sup>

A total of 7782 of 64,190 (12%) women aged 40-79 years with missing values in the questions related to reproduction were excluded. We analyzed 52,289 women aged 40-79 years who had been pregnant, excluding a history of stroke and myocardial infarction at baseline. The exposure was the number of pregnancy losses as follows: no pregnancy loss, 1 pregnancy loss, and  $\geq 2$  pregnancy losses. The number of pregnancy losses was derived from the self-reported questionnaire. The outcome was mortality from total stroke, ischemic stroke, hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage), coronary heart disease, and total CVD. We analyzed all ages and age subgroups (40-59 years and 60-79 years) at baseline.

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