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

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**Grant support**

This research was supported by a grant–in–aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, 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 Life–Style Related Diseases: H20–Junkankitou [Seishuu]‐Ippan–013; Comprehensive Research on Cardiovascular and Life–Style 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 Life-Style 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).

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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**A running title** Pregnancy Loss and Cardiovascular Disease

**Abstract:**

**Purpose**

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/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, tenth version. 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 haemorrhage, and total cardiovascular disease. The multivariable hazard ratio of total cardiovascular disease for ≥2 pregnancy loss versus no pregnancy loss was 0.84 (95% CI, 0.74–0.95). A two-fold excess risk of mortality from

ischemic stroke associated with ≥2 pregnancy loss was observed in women aged 40–59 years, with a multivariable hazard ratio of 2.19 (95% CI, 1.06–4.49), but not in older women.

**Conclusion**

Recurrent 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

## 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 haematological 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 for the risk of CVD, including ischemic stroke and coronary heart disease in women [1]. Additionally, a careful and detailed history of complications in pregnancy by a primary care physician or cardiologist should be taken [1]. However, epidemiological evidence for the risk of complications in pregnancy on long-term CVD is limited in Chinese [2] and Japanese populations [3]. 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 [2]. 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 [3].

Congenital haematological or vascular wall disorders may contribute to the risk of ischemic CVD mortality in younger adults [4–7]. 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 those in older women [8].

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 analysed the data based on the age subgroups of 40–59 years and 60–79 years at baseline.

## Materials and methods

### Study design

The Japan Collaborative Cohort Study was described previously [9]. 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 [9]. Participants were followed up until 2009 in 35 of 45 areas. Follow-up was terminated in 1999 in four areas, in 2003 in four areas, and in 2008 in two areas (median follow-up: 18 years) [9].

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, were annually/biannually confirmed using population registers until the end of the study. These population data were shared with the public health centre and local governmental office [9].

A total of 1,025,703 person-years were followed up for women. Mortality with an identified cause was coded according to the tenth revision of the International Classification of Diseases (ICD-10) [9], including total stroke (I60 to I69) ischemic stroke (I63), haemorrhagic stroke (I60 to I61), intracerebral haemorrhage (I61) subarachnoid haemorrhage (I60), coronary heart disease (I20 to I25), and total CVD

(I01 to 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 [9].

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 analysed 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, one pregnancy loss, and ≥2 pregnancy loss. The number of pregnancy losses was derived from the self-reported questionnaire. The outcome was mortality from total stroke, ischemic stroke, haemorrhagic stroke (intracerebral haemorrhage and subarachnoid haemorrhage), coronary heart disease, and total CVD. We analysed all ages and age subgroups at baseline, 40–59 years, and 60–79 years.

**Statistical analysis**

Analysis of covariance was used to test for differences in age-adjusted means and the prevalence of baseline characteristics. Multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the Cox proportional hazard regression model. Testing for a linear trend across the number of pregnancy losses and

mortality was conducted using a median variable of the number of pregnancy losses (0, 1, or 2). P values <0.05 were considered statistically significant. Kaplan–Meier survival curves were used to model the cumulative mortality. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

**Confounding variables**

We adjusted all analyses for the following confounding variables: age, the number of deliveries, education (primary school, junior high school, high school, college or higher than college), self-reported body mass index (categorized in quintiles), hours of exercise (almost never, or 1–2, 3–4, or ≥5 h/week), hours of walking (seldom, 10–29, 30–59, or ≥60 min/day), smoking status (never, ex-smoker, or current smoker consuming either 1–19 or ≥20 cigarettes/day), and drinking status (never, ex-drinker, or 1–22, 23–45, 46–68, or ≥69 g/day). We considered a history of hypertension and diabetes mellitus as mediators for the association between recurrent pregnancy loss and CVD mortality, and did not include them as adjustment variables for the primary analysis.

**Results**

Table 1 shows age-adjusted mean values for clinical parameters and the

prevalence of cardiovascular risk factors at baseline according to the number of pregnancy losses. Women with ≥2 pregnancy loss were younger (55.8 versus 58.0 years), had a lower number of deliveries (2.6 versus 2.9), had a slightly higher body mass index (23.1 versus 22.9 kg/$m^2$), had higher alcohol consumption (11.7 versus 9.7 g/day), were more likely to smoke (6.6% versus 4.2%), and had a higher prevalence of diabetes (4.3% versus 3.8%) than did women with no pregnancy loss. No significant differences in college or higher education, or physical activity level estimated by walking and exercise habit were observed among the pregnancy loss categories.

Among women aged 40–79 years, the follow-up duration was 160,507, 191,270, and 521,067 person-years for women with ≥2 pregnancy loss, with one pregnancy loss, and without pregnancy loss at baseline, respectively. There were 1240 deaths due to total stroke, 408 due to ischemic stroke, 476 due to haemorrhagic stroke (252 intracerebral haemorrhages and 224 subarachnoid haemorrhages), 538 due to coronary heart disease, and 2815 due to total CVD.

Table 2 shows multivariable HRs for mortality from total stroke, ischemic stroke, haemorrhagic stroke (intracerebral haemorrhage and subarachnoid haemorrhage), coronary heart disease, and total CVD according to the number of pregnancy losses at all ages. The number of pregnancy losses tended to be inversely associated with the

risks of total stroke, intracerebral haemorrhage, and total CVD mortality. The multivariable HR for total stroke mortality in women with one pregnancy loss was 0.91 (95% CI, 0.78–1.06) and that in women with recurrent (≥2) pregnancy loss was 0.84 (95% CI, 0.70–1.02). A similar trend was observed for mortality from intracerebral haemorrhage, with multivariable HRs of 0.88 (95% CI, 0.63–1.23) for one pregnancy loss and 0.68 (95% CI, 0.45–1.03) for recurrent pregnancy loss. With regard to mortality from total CVD, a significant inverse association was observed, with corresponding multivariable HRs of 0.93 (95% CI, 0.84–1.03) and 0.84 (95% CI, 0.74–0.95) , p value for trend <0.001.

Table 3 shows multivariable HRs of mortality from each outcome, stratified by age subgroup. Women aged 40–59 years with ≥2 pregnancy loss had twice the multivariable-adjusted risk of mortality from ischemic stroke than women without pregnancy loss (HR, 2.19; 95% CI, 1.06–4.49). No significant associations were observed for other CVD mortalities. Women aged 60–79 years with pregnancy loss tended to have a lower risk of mortality from total stroke, intracerebral haemorrhage, and total CVD compared with those without pregnancy loss. The multivariable HRs were 0.84 (95% CI, 0.70–1.00) in women with one pregnancy loss and 0.84 (95% CI, 0.68–1.04) in women with recurrent pregnancy loss for total stroke mortality. The

multivariable HRs were 0.70 (95% CI, 0.45–1.08) and 0.63 (95% CI, 0.37–1.09) for intracerebral haemorrhage mortality, and 0.88 (95% CI, 0.78–0.99) and 0.89 (95% CI, 0.77–1.02) for total CVD mortality, respectively. We further adjusted for a history of hypertension and diabetes mellitus for sensitivity analysis, but the results were unchanged (data not shown).

Figure 1 shows Kaplan–Meier survival curves that modelled the cumulative mortality from ischemic stroke at 40–59 years and ischemic stroke at 60–79 years. Women aged 40–59 years with ≥2 pregnancy loss had a greater cumulative mortality from ischemic stroke than those with no or one pregnancy loss, whereas women aged 60–79 years with ≥2 pregnancy loss did not.

**Discussion**

The main findings of the current, large, cohort study are as follows. In women aged 40–79 years, recurrent pregnancy loss was associated with a lower risk of total CVD mortality. Additionally, in younger women aged 40–59 years, recurrent pregnancy loss was associated with a two-fold higher risk of mortality from ischemic stroke.

Pregnancy loss is a comprehensive term, which includes miscarriage, stillbirth, and medically-based termination. Two or more consecutive miscarriages are treated in clinical practice. Approximately 30–50% of these miscarriages are caused by

autoimmune diseases, such as antiphospholipid syndrome, uterine anomalies, or foetal genetic abnormalities [10].

Findings from previous cohort studies on pregnancy loss and cardiovascular disease have been inconsistent. The Chinese cohort study of female workers aged ≥30 years showed that single or multiple spontaneous abortion and miscarriage were not associated with a risk of mortality from ischemic, intracerebral haemorrhage stroke, and ischemic heart disease [2]. German [11] and American [12] cohort studies showed that miscarriage and stillbirth were not associated with a risk of incident stroke, but were associated with a risk of incident ischemic heart disease. Among German women aged 35–48 years who had been pregnant, there was no significant association of ≥1 miscarriage, ≥1 abortion, or ≥1 stillbirth with a risk of incident stroke [11]. However, those who had a history of ≥3 miscarriages or ≥1 stillbirth had a higher risk of incident myocardial infarction, with HRs of 5.06 (95% CI, 1.26–20.29) and 3.43 (95% CI, 1.53–7.72), respectively [11]. Among American women aged 50–79 years who had been pregnant, ≥2 miscarriages and ≥1 stillbirth were associated with a risk of incident coronary heart disease, with HRs of 1.18 (95% CI, 1.04–1.34) and 1.27 (95% CI, 1.07–1.51), respectively, but not ischemic stroke [12]. A Scottish retrospective cohort study showed that women with ≥1 spontaneous abortion prior to a single live birth were at

increased risk of total stroke mortality, with a HR of 1.49 (95% CI, 1.09–2.03) [13]. A Danish population-based cohort study showed that miscarriage and stillbirth were associated with a risk of ischemic stroke, with HRs of 1.16 (95% CI, 1.07–1.25) for miscarriage and 1.74 (95% CI, 1.32–2.28) for stillbirth [8].

We found that women with ≥2 pregnancy loss had a 16% lower risk of total CVD mortality. This reduction in risk may have been due to higher blood concentrations of oestrogen and progesterone compared with women without pregnancy loss. In the current study, the total number of pregnancies of women with ≥2 pregnancy loss was larger than that of women without pregnancy loss. The reason for this finding could be that women with recurrent pregnancy loss attempted to have live birth. The age-adjusted mean (±standard deviation) number of pregnancies was 2.9±1.4 for women without pregnancy loss, 3.6±1.1 for women with one pregnancy loss, and 5.0±1.3 for women with ≥2 pregnancy loss (p for difference <0.001). Blood concentrations of oestrogen and progesterone increase in the early stage of pregnancy and elevate further during the later stage of pregnancy. Production of estradiol-17β is 0.1–0.6 mg/day during non-pregnancy and 15–20 mg/day during pregnancy. Production of estriol is 0.02–0.1 mg/day and 50–150 mg/day, and that of progesterone is 0.1–40 mg/day and 250–600 mg/day, respectively [14]. These sex hormones are protective for development of CVD

through stimulated release of endothelium-derived vasodilator factors and the inhabited renin–angiotensin system [15,16]. Women with recurrent pregnancy loss may have higher levels of oestrogen and progesterone compared with those without pregnancy loss, which may lead to a decreased risk of CVD.

A potential reason for the excess risk of incidence and mortality from ischemic heart disease or stroke in Europeans [8,11–13,17,18] and Israelis [19] is expectant management as the common cost-effective treatment of incomplete abortion in Western and Middle Eastern countries. Expectant management takes more time to complete abortion than does surgical evacuation, which is common in Japan [20]. Expectant management also generally increases the risk of incomplete miscarriage in which sustained immune responses may persist for weeks [21]. This situation might offset partially the protective effect of sex hormones against CVD.

We speculate that women aged 40–59 years with ≥2 pregnancy loss who had an increased risk of ischemic stroke mortality had higher concentrations of oestrogen than those without pregnancy loss. Our finding is supported by a finding from a previous clinical trial of women aged 50–79 years [22]. In this trial, the HR of ischemic stroke associated with oestrogen use was 2.62 (95% CI, 1.01–6.81) for menopause for <10 years, 1.66 (95% CI, 0.97–2.82) for those with menopause for 10–20 years, and 1.32

(95% CI, 0.93–1.87) for those with menopause for >20 years [22]. Other explanations for an excess risk of ischemic stroke mortality associated with ≥2 pregnancy loss in younger women include protein S, antiphospholipid symptoms, preeclampsia or eclampsia, and reversible cerebral vasoconstriction syndrome (RCVS).

A Dutch retrospective family cohort study showed an approximately five-fold increased risk of arterial thromboembolism in individuals with deficiency of protein S (a cofactor for activated protein C) or protein C compared with those without this deficiency at <55 years, but not at ≥55 years [23]. The prevalence of protein S gene mutation leading to a reduction or deficiency in protein S is 10 times higher in the general Japanese population than in Caucasians (2% versus 0.2%) [24–26]. Protein S deficiency is five to 10 times more frequent in Japanese patients (20%) [27] than in Caucasian patients with deep venous thrombosis (2–4%) [28].

Antiphospholipid syndrome is implicated in miscarriage and ischemic stroke in young adults [6]. However, the prevalence of antiphospholipid syndrome in Japan is currently unknown. Patients with antiphospholipid syndrome have anticardiolipin antibodies [4]. These antibodies bind to phospholipids or phospholipid-binding proteins of platelet/endothelial cell membranes, enhance blood coagulation, and increase the risk of venous and arterial embolism [5,6]. A total of 18% of Italians with transient ischemic

attack or ischemic stroke, aged 15–44 years, are positive for antiphospholipids [6]. A total of 81% of British women with a previous arterial or venous thrombotic event and antiphospholipid syndrome have experienced pregnancy loss [10].

Preeclampsia or eclampsia is likely to cause clotting activation by vasospasm [29]. The prevalence of preeclampsia is 3% to 5% in pregnant women and that of eclampsia is 0.05% to 0.93% [29]. Preeclampsia/eclampsia is associated with a risk of ischemic stroke [1].

Another clinical manifestation of vasospasm is RCVS, which is a cerebral manifestation of Raynaud's phenomenon and is characterized by thunderclap headache, with or without other acute neurological symptoms [30]. Ischemic stroke is one of the complications of RCVS [30]. Clinical reports of 77 Taiwanese [31], 139 American [32], 67 French [33], and three Japanese people [34] showed that the incidence of RCVS peaks at approximately 42 years of age and is more common in women than in men [29]. However, the incidence of RCVS is unknown in the general population [30]. Patients with autoimmune disorders, including antiphospholipid syndrome, are particularly susceptible to RCVS and ischemic stroke at young ages [33].

**Strengths and Limitations**

Strengths of our study are that it was a large prospective cohort with long-term

follow-up, and multiple outcomes. There are some limitations in the current study. First, a self-reported questionnaire consisting of simple questions related to reproduction was used at baseline. The validity and reliability of the question regarding reproductive history could not be evaluated. Reproductive history, including a history of abortion, is particularly sensitive, particularly by consultation. The sensitivity for self-reported induced abortion is 70%, which remains higher than that of interview-based reporting of abortion (30%–50%) [35]. Second, ischemic stroke mortality in the younger age group might be related to chance because there was a small number of cases in this age group.

In conclusion, recurrent pregnancy loss tended to be associated with lower risk of cardiovascular disease mortality in aged 40–79 years while younger women aged 40–59 years had a two-fold higher risk of ischemic stroke mortality associated with recurrent pregnancy loss.

**Acknowledgments**

The authors are grateful to all of the participants in each cohort study. The authors appreciate all of the staff members involved in this study for their help in conducting the baseline survey and follow-up. The authors also thank Dr. Miho Muraji, Dr. Daita Kaneda, and Dr. Takashi Takeda for their professional comments.

**Ethical Considerations:**

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.

**References:**


1. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al.: Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011 Mar 22;57:1404–23.

2. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, et al.: Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. Int J Epidemiol 2011;40:1510–1518.

3. Sugiura-Ogasawara M, Suzuki S, Ozaki Y, Katano K, Suzumori N, Kitaori T: Frequency of recurrent spontaneous abortion and its influence on further marital relationship and illness: The Okazaki Cohort Study in Japan. J Obstet Gynaecol Res 2013;39:126–131.

4. Hughes G: The antiphospholipid syndrome: Ten years on. Lancet 1993;342:341–344.

5. Matyja-Bednarczyk A, Swadźba J, Iwaniec T, Sanak M, Dziedzina S, Ćmiel A, et al.: Risk factors for arterial thrombosis in antiphospholipid syndrome. Thromb Res 2014;133:173–176.

6. Nencini P, Baruffi MC, Abbate R, Massai G, Amaducci L, Inzitari D: Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. Stroke 1992;23:189–193.

7. Su M-T, Lin S-H, Chen Y-C: Genetic association studies of angiogenesis- and vasoconstriction-related genes in women with recurrent pregnancy loss: a systematic review and meta-analysis. Hum Reprod Update 2011;17:803–12.

8. Ranthe M, Andersen EA, Wohlfahrt J, Bundgaard H, Melbye M, Boyd H: Pregnancy Loss and Later Risk of Atherosclerotic Disease. Circulation 2013;127:1775–1782.

9. Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, et al.: Cohort Profile of the Japan Collaborative Cohort Study at Final Follow-up. J Epidemiol 2013;23:227–232.

10. Branch DW, Gibson M, Silver RM: Clinical practice. Recurrent miscarriage. N Engl J Med 2010;363:1740–7.

11. Kharazmi E, Dossus L, Rohrmann S, Kaaks R: Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart 2011 Jan;97:49–54.

12. Parker DR, Lu B, Sands-Lincoln M, Kroenke CH, Lee CC, O'Sullivan M, et al.: Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. Ann Fam Med 2014 Jul;12:302–9.

13. Smith G, Pell J, Walsh D: Spontaneous loss of early pregnancy and risk of ischemic heart disease in later life: retrospective cohort study. Bmj 2003;423–424.

14. Cunningham FG, Leveno K, Bloom S, Hauth J, Rouse D, Spong C: Williams Obstetrics: 23rd Edition. New York, McGraw-Hill Professional, 2009.

15. Virdis A, Taddei S: Endothelial aging and gender. Maturitas 2012 Apr;71:326–30.

16. Dos Santos RL, Da Silva FB, Ribeiro RF, Stefanon I: Sex hormones in the cardiovascular system. Horm Mol Biol Clin Investig 2014;18:89–103.

17. Kharazmi E, Fallah M, Luoto R: Miscarriage and risk of cardiovascular disease. Acta Obstet Gynecol Scand 2010;89:284–288.

18. Maino A, Siegerink B, Algra A, Martinelli I, Peyvandi F, Rosendaal FR: Pregnancy loss and risk of ischemic stroke and myocardial infarction. Br J Haematol 2016 Jul;174:302–9.

19. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Holcberg G, Sheiner E: Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity? Am J Obstet Gynecol 2014;211:414.e1-414.e11.

20. Minakami H, Hiramatsu Y, Koresawa M, Fujii T, Hamada H, Iitsuka Y, et al.: Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2011 edition. J Obstet Gynaecol Res 2011;37:1174–1197.

21. Nanda K, Lopez LM, Grimes D a, Peloggia A, Nanda G: Expectant care versus surgical treatment for miscarriage. Cochrane database Syst Rev 2012;CD003518.

22. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard B V, Kooperberg C, Rossouw JE, et al.: Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. Circulation 2006 May 23;113:2425–34.

23. Mahmoodi B, Brouwer J, Veeger NM, van der Meer J: Hereditary Deficiency of Protein C or Protein S Confers Increased Risk of Arterial Thromboembolic Events at a Young Age: Results From a Large Family Cohort Study. Circulation 2008;118:1659–1667.

24. Beauchamp NJ, Dykes AC, Parikh N, Tait RC, Daly ME: The prevalence of, and

molecular defects underlying, inherited protein S deficiency in the general population. Br J Haematol 2004;125:647–654.

25. Nomura T, Suehisa E, Kawasaki T, Okada A: Frequency of protein S deficiency in general Japanese population. Thromb Res 2000;100:367–371.

26. Sakata T, Okamoto A, Mannami T, Tomoike H, Miyata T: Prevalence of protein S deficiency in the Japanese general population: The Suita study. J Thromb Haemost 2004;2:1012–1013.

27. Kinoshita S, Iida H, Inoue S, Watanabe K, Kurihara M, Wada Y, et al.: Protein S and protein C gene mutations in Japanese deep vein thrombosis patients. Clin Biochem 2005;38:908–915.

28. Rodeghiero F, Tosetto A: The epidemiology of inherited thrombophilia: the VITA Project. Vicenza Thrombophilia and Atherosclerosis Project. [Internet]. . Thromb Haemost 1997;78:636–40.

29. Bellamy L, Casas J, Hingorani A, Williams D: Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.

30. Ducros A: Reversible cerebral vasoconstriction syndrome. Handb Clin Neurol

2014;121:1725–41.

31. Chen S-P, Fuh J-L, Wang S-J, Chang F-C, Lirng J-F, Fang Y-C, et al.: Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. Ann Neurol 2010 May;67:648–56.

32. Singhal AB, Hajj-Ali RA, Topcuoglu MA, Fok J, Bena J, Yang D, et al.: Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 2011 Aug;68:1005–12.

33. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser M-G: The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 2007 Dec;130:3091–101.

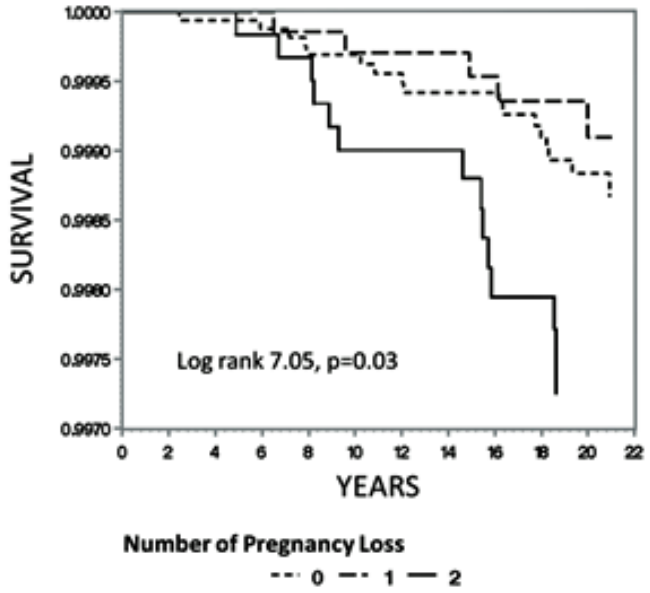
34. Ishi Y, Sugiyama T, Echizenya S, Yokoyama Y, Asaoka K, Itamoto K: Reversible cerebral vasoconstriction syndrome associated with stroke: three case reports (in Japanese). [Internet]. . No Shinkei Geka 2014;42:129–36.

35. Udry BJR, Gaughan M, Schwingl PJ, Berg BJ Van Den: Research notes. Fam Plann Perspect 1996;228–231.

**Figure legend**

**Figure. 1** Kaplan–Meier survival curves for mortality of (a) ischemic stroke in women aged 40–59 years and (b) ischemic stroke in women aged 60–79 years.

**a. Ischemic stroke aged 40–59 years**




**b. Ischemic stroke aged 60–79 years**

**Table 1. Age-adjusted mean values and prevalence of cardiovascular risk factors at baseline according to the number of pregnancy loss.**

| | Number of pregnancy loss | | |
|---|---|---|---|
| | None | 1 | ≥2 |
| Number of patients | 31321 | 11312 | 9656 |
| Person-years | 521067 | 191270 | 160507 |
| Age, years (SE) | 58.0 (0.1) | 55.8 (0.1)‡ | 55.8 (0.1)‡ |
| The number of deliveries (SE) | 2.9 (0.01) | 2.6 (0.01)‡ | 2.6 (0.01)‡ |
| College or higher education, n (%) | 23199 (9.4) | 8906 (11.1)‡ | 7874 (10.2) |
| Body mass index, $kg/m^2$ (SE) | 22.9 (0.02) | 22.9 (0.03) | 23.1 (0.03)‡ |
| Exercise ≥5 h/week, n (%) | 25384 (4.9) | 9647 (4.0) | 8293 (4.1) |
| Walking ≥1 h/day, n (%) | 24094 (52.1) | 9068 (52.0) | 7865 (51.3) |

| | | | |
|---|---|---|---|
| Current smoker, n (%) | 27383 (4.2) | 10044 (4.9)* | 8585 (6.6)‡ |
| Ethanol consumption, g/day (SE) | 9.7 (0.2) | 9.5 (0.3) | 11.7 (0.3)‡ |

Analysis of covariance was used to test for differences from no pregnancy loss with adjustment for age. *p<0.05, †p<0.01, ‡p<0.001.

SE, standard error.

**Table 2. Multivariable hazard ratios (HRs, 95% CI) of cardiovascular disease mortality according to the number of pregnancy loss in women aged 40–79 years.**

| | | Number of pregnancy loss | | | |
|---|---|---|---|---|---|
| | | None | 1 | ≥2 | P for trend |
| | Person years | 521067 | 191270 | 160507 | |
| Total stroke mortality | Number of deaths | 901 | 205 | 134 | |
| | Multivariable HR (95% CI) | 1.00 | 0.91 (0.78–1.06) | 0.84 (0.70–1.02) | 0.01 |
| Ischemic stroke mortality | Number of deaths | 302 | 65 | 41 | |
| | Multivariable HR (95% CI) | 1.00 | 0.96 (0.73–1.26) | 0.95 (0.68–1.33) | 0.32 |
| Hemorrhagic stroke mortality | Number of deaths | 325 | 90 | 61 | |
| | Multivariable HR (95% CI) | 1.00 | 0.95 (0.75–1.21) | 0.83 (0.63–1.10) | 0.15 |

| | | | | | |
|---|---|---|---|---|---|
| Intracerebral hemorrhage mortality | Number of deaths | 181 | 45 | 26 | |
| | Multivariable HR (95% CI) | 1.00 | 0.88 (0.63–1.23) | 0.68 (0.45–1.03) | 0.05 |
| Subarachnoid hemorrhage mortality | Number of deaths | 144 | 45 | 35 | |
| | Multivariable HR (95% CI) | 1.00 | 1.04 (0.74–1.45) | 1.01 (0.69–1.47) | 0.93 |
| Coronary heart disease mortality | Number. of deaths | 388 | 94 | 56 | |
| | Multivariable HR (95% CI) | 1.00 | 1.00 (0.79–1.25) | 0.84 (0.63–1.12) | 0.08 |
| Total cardiovascular disease mortality | Number of deaths | 2048 | 471 | 296 | |
| | Multivariable HR (95% CI) | 1.00 | 0.93 (0.84–1.03) | 0.84 (0.74–0.95)† | <0.001 |

Multivariable-adjusted for: age, the number of deliveries, education, body mass index, exercise hours, walking hours, smoking status, and drinking status.

Test for difference from no pregnancy loss: †$p < 0.01$.

HR, hazard ratio

**Table 3. Multivariable hazard ratios (HRs, 95%CI) of cardiovascular disease mortality according to the number of pregnancy loss, stratified by age subgroup.**

| | | Number of pregnancy loss | | | |
|---|---|---|---|---|---|
| | | None | 1 | ≥2 | P for trend |
| **40-59 years** | Person years | 304652 | 130191 | 111803 | |
| Total stroke mortality | Number of deaths | 105 | 56 | 39 | |
| | Multivariable HR (95% CI) | 1.00 | 1.26 (0.91–1.75) | 0.95 (0.66–1.38) | 0.96 |
| Ischemic stroke mortality | Number of deaths | 17 | 6 | 14 | |
| | Multivariable HR (95% CI) | 1.00 | 0.86 (0.34–2.18) | 2.19 (1.06–4.49)* | 0.05 |
| Hemorrhagic stroke mortality | Number of deaths | 74 | 43 | 22 | |
| | Multivariable HR (95% CI) | 1.00 | 1.36 (0.93–1.98) | 0.76 (0.47–1.22) | 0.69 |

| | | | | | |
|---|---|---|---|---|---|
| Intracerebral hemorrhage mortality | Number of deaths | 37 | 21 | 11 | |
| | Multivariable HR (95% CI) | 1.00 | 1.33 (0.78–2.28) | 0.77 (0.39–1.52) | 0.55 |
| Subarachnoid hemorrhage mortality | Number of deaths | 37 | 22 | 11 | |
| | Multivariable HR (95% CI) | 1.00 | 1.39 (0.82–2.36) | 0.74 (0.37–1.46) | 0.60 |
| Coronary heart disease mortality | Number of deaths | 43 | 24 | 10 | |
| | Multivariable HR (95% CI) | 1.00 | 1.29 (0.78–2.13) | 0.56 (0.28–1.11) | 0.22 |
| Total cardiovascular disease mortality | No. of deaths | 238 | 119 | 74 | |
| | Age-adjusted HR (95% CI) | 1.00 | 1.17 (0.94–1.45) | 0.79 (0.61–1.02) | 0.09 |
| | Multivariable HR (95% CI) | 1.00 | 1.18 (0.94–1.47) | 0.77 (0.60–1.02) | 0.17 |
| | | | | | |
| **60-79 years** | Person years | 216415 | 61079 | 48704 | |
| Total stroke mortality | Number of deaths | 796 | 149 | 95 | |

| | | | | | |
|---|---|---|---|---|---|
| | Multivariable HR (95% CI) | 1.00 | 0.84 (0.70–1.00)* | 0.84 (0.68–1.04) | 0.002 |
| Ischemic stroke mortality | Number of deaths | 285 | 59 | 27 | |
| | Multivariable HR (95% CI) | 1.00 | 0.99 (0.75–1.32) | 0.77 (0.51–1.15) | 0.08 |
| Hemorrhagic stroke mortality | Number of deaths | 251 | 47 | 39 | |
| | Multivariable HR (95% CI) | 1.00 | 0.77 (0.56–1.05) | 0.89 (0.63–1.26) | 0.11 |
| Intracerebral hemorrhage mortality | Number of deaths | 144 | 24 | 15 | |
| | Multivariable HR (95% CI) | 1.00 | 0.70 (0.45–1.08) | 0.63 (0.37–1.09) | 0.02 |
| Subarachnoid hemorrhage mortality | Number of deaths | 107 | 23 | 24 | |
| | Multivariable HR (95% CI) | 1.00 | 0.85 (0.54–1.34) | 1.21 (0.77–1.90) | 0.88 |
| Coronary heart disease mortality | Number of deaths | 345 | 70 | 46 | |
| | Multivariable HR (95% CI) | 1.00 | 0.94 (0.72–1.22) | 0.98 (0.72–1.35) | 0.25 |

| | | | | | |
|---|---|---|---|---|---|
| Total cardiovascular disease mortality | Number of deaths | 1810 | 352 | 222 | |
| | Multivariable HR (95% CI) | 1.00 | 0.88 (0.78–0.99)* | 0.89 (0.77–1.02) | <0.001 |

Multivariable-adjusted for: age, the number of deliveries, education, body mass index, exercise hours, walking hours, smoking status, and drinking status.

Test for difference from no pregnancy loss: *$p < 0.05$.

HR, hazard ratio