博士論文

Female reproductive factors and risk of all-cause and cause-specific mortality among women: The Japan Public Health Center-based Prospective Study (JPHC Study)

（日本人女性の生殖関連要因と全死亡および主要死因別死亡の関連に関する研究

（多目的コホート研究））

大月　詩織

Shiori Otsuki

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Shiori Otsuki

(41-167103)

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Supervisor: Professor Kenji Shibuya

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Abstract

Objective: Reproductive events and their accompanying fluctuations in sex hormones lead to a series of physiological and psychological changes throughout life in women. Numerous long-term studies have investigated the impact of reproductive events on women's health. Nevertheless, the potential link between reproductive factors and mortality is not necessarily fully understood. This study investigated the association between reproductive history and mortality from all and major causes among Japanese women.

Methods: Data from a large-scale population-based cohort study in Japan was used. After excluding ineligible subjects, 59,983 women aged 40 to 69 years were followed from enrolment (1990-1993) until the end of 2014. A multivariable-adjusted Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CI) for all-cause and leading cause of mortality, with adjustment for potential confounders.

Results: Regarding all-cause and cause-specific mortality, after a mean follow-up of 20.9 years of 40,149 women (840.375 person-years), 4,788 total deaths were identified. Inverse associations with all-cause mortality were found in parous women [0 .74 (0.67–0.82)], women with two or three births compared with a single birth [2 births: 0.88 (0.78–0.99); 3 births: 0.83 (0.74–0.94)], parous women who breastfed [0.81 (0.75–0.87)], women who were older at menopause [0.88 (0.80–0.97); P_{trend}: <0.01] and women who had a longer fertility span [0.85 (0.76–0.95); P_{trend}: <0.01]. A positive association was seen between all-cause mortality and later age at first birth (≥30 years) than early childbearing (≤ 22 years). For external causes of death, during 1,028,583 person-years of follow-up in 49,279 eligible subjects (average 20.9 years of follow-up), 328 deaths by all injuries were identified. Among parous women, ever versus never breastfeeding was associated with a decreased risk of all injuries [0.67 (0.49–0.92)]. Risk of suicide was inversely associated with ever versus never parity [0.53 (0.32–0.88)] and three births [reference: 2 births; 0.61 (0.39–0.97)]. A lower risk of death by accidents was seen in ever breastfeeding compared to never breastfeeding [0.63 (0.40–0.97)].

Conclusion: This study suggests that parous, two or three births, breastfeeding, late age at menopause and longer reproductive span are associated with lower risk of all-cause and cause-specific mortality among Japanese women.

Keywords: Reproductive factors, parity, age at first birth, breastfeeding, age at menarche, length of menstrual cycle, exogenous hormone use, menopausal status, age at menopause, total fertility span, mortality, prospective cohort study, Japan

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This thesis would never have come about had it not been for the support from all of the people mentioned.

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CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardio Vascular Disease
HR	Hazard Ratio
HT	Hormone Therapy
ICD-10	International Classification of Diseases, 10th edition
MAR	Missing At Random
MCAR	Missing Completely At Random
MHLW	Ministry of Health, Labour and Welfare
MI	Multiple Imputation
MICE	Multiple Imputation by Chained Equation
MNAR	Missing Not At Random
NCDs	Non-Communicable Diseases
OCs	Oral Contraceptives
OECD	Organization for Economic Cooperation and Development
PHC	Public Health Center
WHO	World Health Organization

1. INTRODUCTION

1.1. Organization of the thesis

This thesis consists of five chapters. Chapter 1 provides an overview of the risk factors for mortality risk and the leading causes of death among Japanese women followed by the rationality and objective of this project. The methods, results, and summary findings for all-cause and internal cause of death according to reproductive factors are described in Chapter 2. Those for external cause of death are outlined in Chapter 3. In Chapter 4, the findings of this study are compared with previous evidence, and strengths and limitations are discussed. Chapter 5 summarizes the entire thesis, highlights the contribution of this study, and gives ideas for further research.

1.2. Background

Although gender differences in mortality rate and life expectancy vary by region, women exhibit greater life expectancy in most countries as well as in the Japanese population. Globally, while increased longevity is observed in both sexes, the difference in average life expectancy between men and women have remained the same at all time periods [1]. Therefore, numerous studies have been driven to elucidate factors that make women live longer than men.

1.2.1. Major risk factors associated with mortality

As countries develop, the patterns of the leading causes of death typically shift from infectious diseases toward non-communicable diseases (NCDs) [2]. This epidemiological transition can occur because of improvements in clinical care, public health interventions, aging, and changes in exposure levels to risk factors to specific diseases [2, 3].

Numerous early studies have investigated and proposed lifestyle as being responsible for preventable deaths in most countries [4-6]. In particular, smoking [7], alcohol [8], physical activity [9, 10], dietary consumption [11-13], body composition [14], and the combined effects of these factors [3, 15] are the most frequently quoted factors influencing one's chances of premature death [3, 16]. Furthermore, each factor has its own specific causes as well, generating multiple paths to influence events over time [3, 17]. Examples include socioeconomic status [18, 19], environmental conditions [16, 20], cultural and social settings [21-24], and interpersonal relationships [25]. Additional factors which affect avoidable death include illicit drug use, exposure to hazardous chemical substances, and occupational exposure [3].

Studies comparing a comprehensive list of risk factors identified smoking and high blood pressure as the two major risk factors for mortality from non-communicable diseases and injuries in Japan [26]. These estimations are comparable with that of the global trend [3]. Advances in medical care and health strategy could be responsible for the increase in life expectancy in the whole Japanese population [24]. However, the trends in leading causes of death and in life expectancy are apparently different between men and women. One possible explanation is the discrepancy in the prevalence and exposure level of risk factors: men engage more frequently in risk behaviors such as smoking and alcohol consumption, and hazardous occupation than women [27-30].

1.2.2. Effects of female sex steroids on mortality

Another proposed reason for the higher longevity in women is genetic and physiological factors, including X chromosome and sex steroid hormones [31]. Sex hormones, which are responsible for the sexual features of an organism, have various effects on several tissues through interaction with their receptors. In particular, the multiple cardioprotective effects of estrogen are well-known [32]: this hormone leads to a lower rate of incidence and mortality of cardiovascular disease in women compared to the counterpart in men [33]. While the gender gap in circulatory disease is apparent and persists throughout life, the gap becomes narrow over time after the onset of menopause [33]. Menopause may change the likelihood of development of cardiovascular disease independent of age because of the dramatic decline in endogenous sex steroids.

Variation in the incidence rate before and after menopause point to a vital role for endogenous sex hormones in the etiology of cancers of the reproductive organ [34, 35]. In particular, estrogen is considered to be the main risk factor for estrogen-responsive cancers [36]. Pregnancy and subsequent breastfeeding are considered to be protective against breast and gynecological cancers, through inhibition of ovulation during this period [36]. The delayed final maturation of breast cells is another mechanism of breast cancer development in nulliparous women [36].

Lifestyle-related factors may further modify the levels of endogenous sex hormones. Smoking may offset the benefits from sex steroids because of the effects of an antiestrogen and a possible induced premature menopause [37-39]. A precursor of estrogen is increased with alcohol intake as a consequence of adrenal secretion [39]. Estradiol controls the typical distribution of body fat and adipose tissue metabolism; conversely, however, adipose tissue becomes the primary source of estrogen after menopause [40]. Therefore, lifelong changes in sex steroids and environmental factors could mutually influence and modulate the likelihood of mortality.

1.2.3. Leading causes of death among Japanese women

The trends in the leading causes of death for women are presented in Figures 1-1 [41]. Although cancer, heart disease, and stroke remain the top three causes of death, they show differing trends. Stroke was the top cause of death in Japan until 1983, but its mortality rate then gradually declined before leveling off between 1985 and 2010. Cancer mortality surpassed stroke in 1983 and continued to increase, with the result that it remained the leading cause of death for two decades. The mortality rate

of heart disease and pneumonia has shown an upward trend, but the rate of increase is higher for pneumonia than heart disease. Although fluctuations are seen in the rate of death by senility, accidents, and suicide, these nevertheless remain the same over time compared with the top four leading causes of death. The temporary decline of heart disease mortality rate in 1995 was due to the adoption of the International Classification of Diseases, 10th edition (ICD-10) and the international rules for selecting the underlying cause of death for primary mortality. Because physicians in Japan diagnosed sudden death or death in the end stages as heart failure, the adoption of ICD-10 caused a decline in mortality rate from heart disease [42].

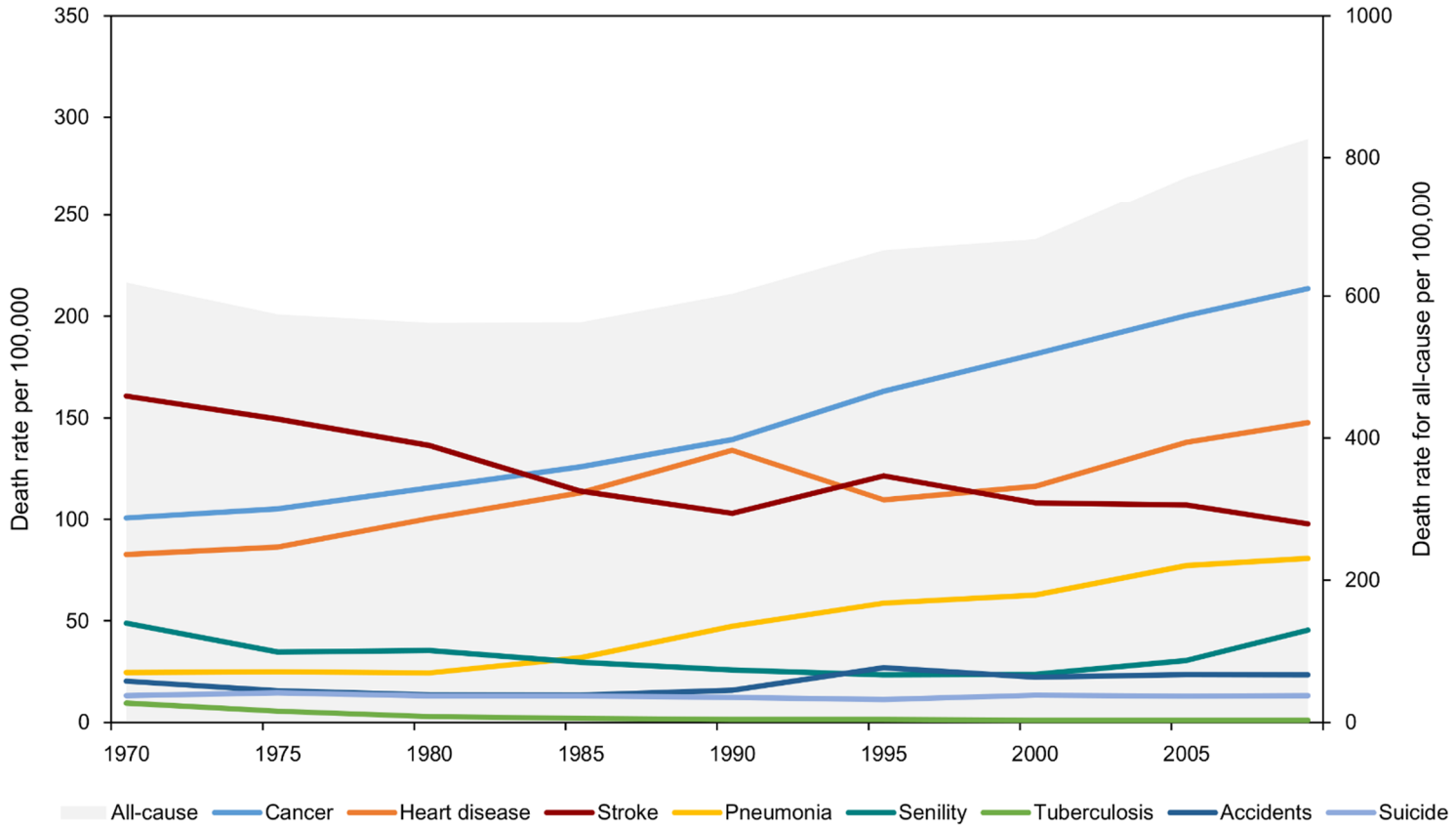


Figure 1-1: Trends in leading causes of death in women: Japan, 1970-2010

Source: The Vital Statistics in Japan. Ministry of Health, Labour and Welfare, 2017[41]

In terms of site-specific cancer as a cause of death, stomach cancer was the leading cause of death in women until the early 1990s (Figure 1-2) [41]. The increasing trend in mortality from lung, colorectal, pancreatic, and breast cancers may partly be a consequence of a change in lifestyle and increased exposure to risk factors such as smoking [36, 43, 44]. In contrast, the decreasing trend seen in stomach and liver cancer could be strongly associated with environmental improvement against infectious agents such as H. pylori, and hepatitis B and C viruses [26].

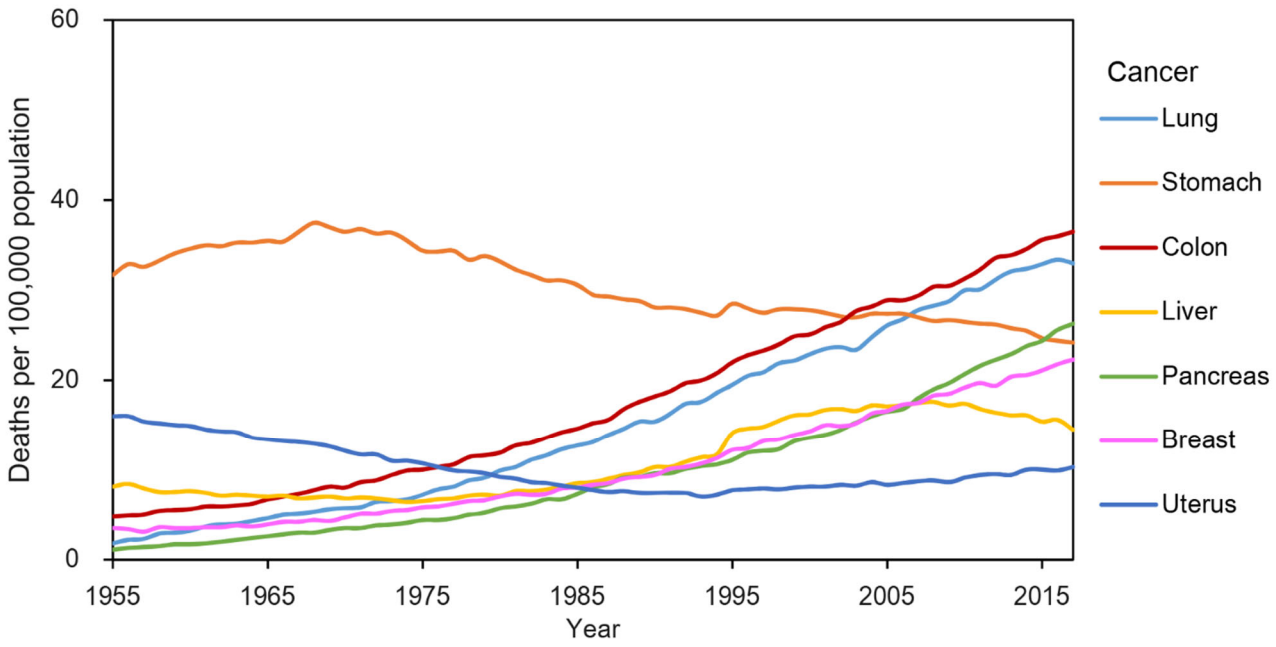


Figure 1-2: Site-specific mortality by cancer death in women per 100,000: Japan, 1955-2017
Source: The Vital Statistics in Japan. Ministry of Health, Labour and Welfare (2017) [41]

Figure 1-3 compares life expectancy in women in 1990 and 2015 and the leading causes of death in selected countries, ranked in order of the life expectancy in 2015 [45]. Blue colors in a bar mean death by non-communicable diseases, while green means death by external causes, and red means death by communicable disease, maternal and child health, and nutrition problems. Japan has enjoyed the longest life expectancy for decades. Most of the leading causes of death in Japan are non-communicable disease, as is also the case in other developed countries, including Australia, France, the United Kingdom and the United States.

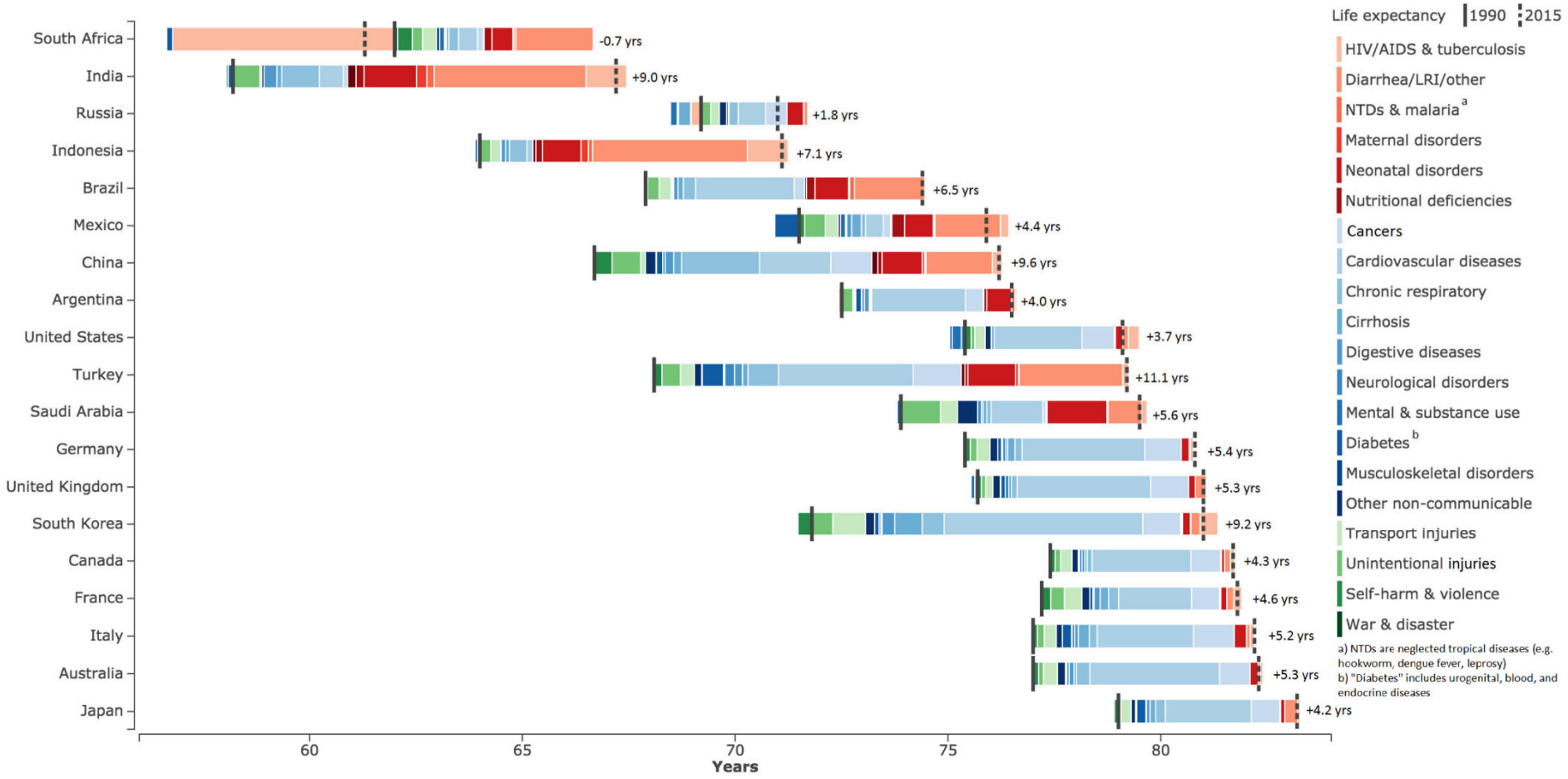


Figure 1-3: Change in country life expectancy and probability of death in women: 1990-2015
Source: Institute for Health Metrics and Evaluation (2015) [45]

When focusing on the trends in mortality from all and breast cancers, Japan, China and South Korea remain with an increasing or stable trend in breast cancer, whereas other Western countries have been experiencing downward trends (Figure 1-4) [46]. Time lags in mortality from breast cancer between Asian and Western countries may be due, in part, to a change to a westernized lifestyle, resulting in convergence toward the risk factor profile of Western countries [47].

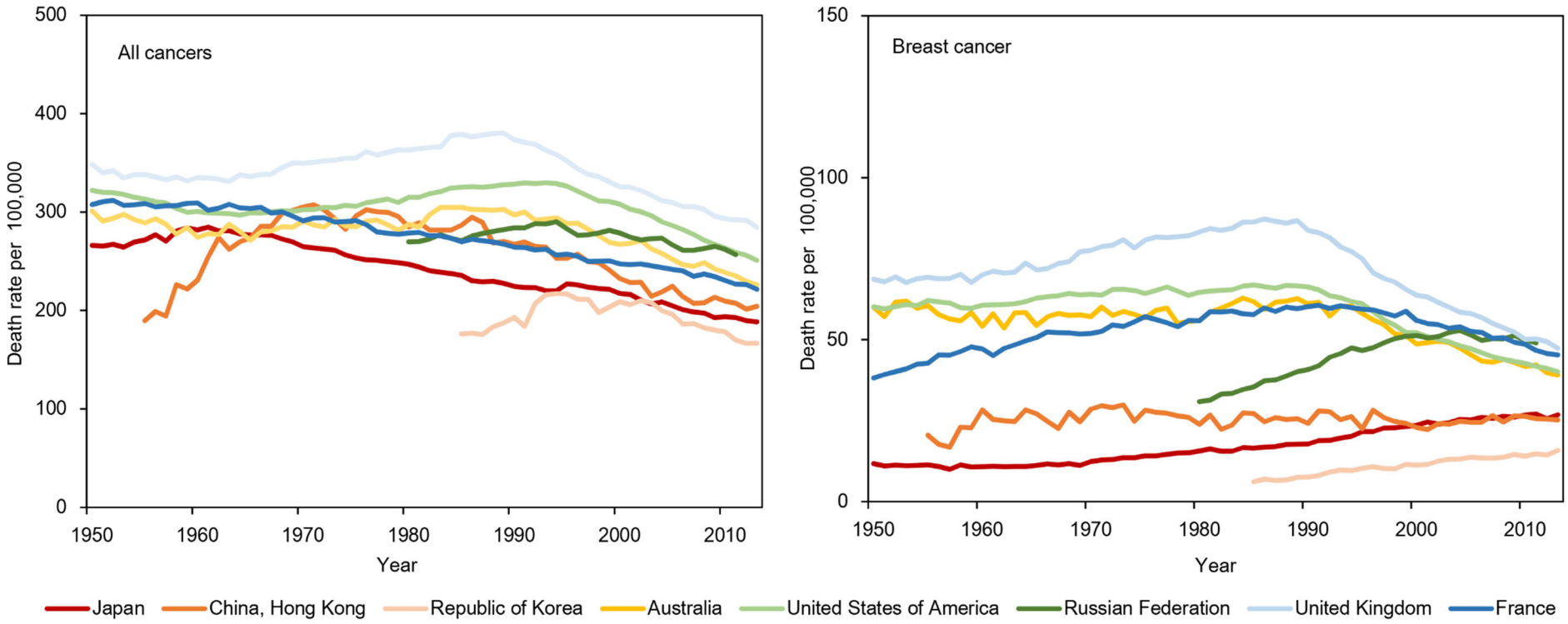


Figure 1-4: Comparison between selected countries for trends in the all cancer (left) and breast cancer (right), 1950-2010

Source: International Agency for Research on Cancer [46]

1.3. Rational and objectives of the study

Reproductive events and their accompanying fluctuations in sex hormones in women lead to a series of physiological and psychological changes throughout life. Although numerous long-term studies have investigated the impact of reproductive events on women's health, the potential link between reproductive factors and mortality is not necessarily fully understood. Most of the reproductive factors are not modifiable, which may be one reason for their not receiving as much attention as lifestyle-related factors. Nevertheless, these factors are common risk predictors for most women regardless of region or ethnicity. As reproductive factors are intricately linked with several diseases, analysis of reproductive parameters on mortality risk could provide further insights to clarify the higher longevity of women and women's long-term health.

As a further complication, since most studies have been conducted in Western countries, it is unclear to what extent these associations relate to Asian populations. Specifically, the association between reproductive factors, other than age at menarche, and risk of all-cause and cause-specific mortality has not been reported from the Japanese population. Asian women, including Japanese women, have different menstrual and reproductive patterns as well as various lifestyle factors than women living in Western countries. The fact that Japan has the highest life expectancy is another motivating reason to focus on Japanese women.

1.3.1. All-cause and internal causes of death

Previous epidemiological studies on the association between reproductive factors and all-cause and cause-specific mortality have shown inconsistent results (Table 1-1). Some [48-53] but not all studies [54-57] reported a U-shaped pattern between parity and risk of all-cause mortality. This inconsistency is possibly due to varying definitions of subjects and categorization of parity across studies. Although previous studies reported the association between breastfeeding and cardiovascular disease mortality, few studies have examined the association between breastfeeding and risk of all-cause or mortality from other major causes of death [50, 55]. Later age at first birth is associated with an elevated risk of breast cancer mortality, but results for the association with the risk of all-cause and circulatory disease mortality vary substantially [50, 55, 57, 58].

Most studies have reported an increased risk of mortality from all-cause or/and cancer and circulatory disease with early onset of menarche [55, 59-62]. Although this is hypothesized due to both early and more prolonged exposure to sex hormones, few studies have simultaneously examined the association between mortality risk and ovulatory lifespan, which is the total number of years with ovulation, from menarche until menopause [55, 59]. Post-menopausal women have a potentially higher risk of mortality independent of age, but few studies have analysed this idea with stratification by menopausal status.

Table 1-1: Summary of previous studies on the association between reproductive factors and all-cause mortality

References (country or study)	Population	Age	Cases (n)	Ever parity	Increasing parity	Late age at first birth	Ever breast-feeding	Late menarche	Late menopause	Long fertility span	OCs use
Gaudet et al.[50] [a] 2017 (US)	424,797	45-94	238,324	↓	U-shape	↑					
Zheng et al.[53] 2016 (systematic review)	2,813,418	30-90	NA	↓	U-shape						
Muka et al.[63] 2016 (Systematic review)	109,898	NA	31,427						↓		
Charalampopulos et al.[62] 2014 (Systematic review)	152,747	26-103	48,970					↓			
Merritt et al.[55] 2015 (EPIC)	322,972	25-75	14,383	↓	J-shape	U-shape	↓	↓	↓	NA	↓
Charlton et al. [64] 2014 (US)	121,577	30-55	31,286								NA
Wu et al. [59] [a] 2014 (China)	31955	40-70	3,158					↓	↓	NA	
Jacobsen et al. [52] [a] 2011 (US)	19,688	25+	3,122		NA			↓			
Vessey et al. [56] 2010 (UK)	17,032	25-39	1,715		NA						↓
Grundy et al. [57] 2010 (Norway)	744,784	45-68	23,241		↓	↓					
Hannaford et al. [65] 2010 (UK)	46,112	<39	4,611								↓
Graff t al. [66] 2006 (Norway)	20,282	20-49	518								NA

[a] Menopausal women only; ↓ : decreased risk or decreasing trend of risk; ↑ : increased risk or increasing trend of risk; U-shape: U-shaped non-linear association; J-shape: J-shaped non-linear association; NA: null association

1.3.2. External causes of death

Globally, more than five million people die each year as a result of external causes, and it has become a major public health concern [67]. Leading causes of injuries include road traffic accidents, falls, suicide, and other unintentional injuries [67]. In Japan, suicide and accidents accounted for two of the top 10 causes of death among women aged 10-79 years in 2017 [68]. Japan has been experiencing a slightly decreasing suicide rate since its peak in 1998 [69]. However, more than 20,000 people die annually by suicide, which results in the suicide rate in Japanese women remaining the second highest after Korea among OECD countries [70].

Early epidemiological studies focused on potential associations between reproductive factors, and suicide behaviors and nonfatal accidents, with few studies examining external causes of death. The first report on a possible link between parity and suicide was Durkheim's hypothesis in 1897, which suggested that parenthood was an important factor in protecting against suicide, rather than marriage per se [71]. Reported or proposed protective factors for suicide include being pregnant [72, 73], having children [71, 74], ever or multi parity [75-78], late age at first birth [75], and never use of oral contraceptives (OCs) [64]. Similar results were also noted for deaths by accident [48, 57, 64, 79, 80]. However, these findings remain inconsistent, and a specific mechanism to explain these associations has not been provided, other than regarding parity [64, 65, 78, 81]. To date, no study has comprehensively investigated reproductive factors as potential markers for mortality risk of external causes. Specifically, there is no report on the association between experience of breastfeeding and external cause of death from any country.

Suicide attempts and completion were significantly more frequent at times of low or rapid decline states in endogenous sex steroids (estrogen and progesterone), such as peri-menopause [82], the postpartum period [83], and premenstrual and menstrual phases of the cycle [84, 85]. The complicated interplay among female sex steroids with the neuroregulatory system may link reproductive events to mental illness and suicidality [83, 85, 86]. Since female suicide completers are more likely to have a history of self-harm/suicide attempts [87], even the events that occurred long before, for example, onset at menarche, may be worth considering as risk factors of their lifetime suicidality. Women with a hypoestrogenic period such as menopause may be at increased likelihood of accidents due to a decrease in musculoskeletal [88] and cognitive function [89, 90].

1.3.3. Objectives

This thesis provides evidence from a large population-based prospective study for the impact of female reproductive factors on mortality risk among Japanese women. Because Japanese women have enjoyed the longest life expectancy since 1985, the findings obtained from this study would contribute to clarifying factors associated with women's health and longevity. The originality of this study lies in its suggestion of how reproductive factors modulate the risk of mortality, including external causes of death among women. Therefore, this study aims to:

(1) Evaluate the effect of female reproductive factors associated with risk of all-cause and leading causes of death including cancer, heart disease, stroke, and respiratory disease;

(2) Assess the risk of all-cause and major causes of external death according to female reproductive factors.

2. Female reproductive factors and risk of all-cause and cause-specific mortality among women: JPHC Study

This chapter describes the materials and methods of the study in section 2.1. The results according to all-cause and cause-specific mortality are shown in section 2.2. Lastly, summary of findings are described in section 2.3.

2.1. Methods and materials

2.1.1. Study design

The data from the Japan Public Health Center-based Prospective Study (JPHC Study) was used. This well-designed population-based cohort project is a representative cohort study in Japan. It was launched in late 1980 by the National Cancer Research Institute Japan with approximately 140,000 participants. This project aims to elucidate risk and preventive factors for cancer and cardiovascular diseases in the Japanese population, contribute to public health policy making, and promote better health in the Japanese population. This project has now expanded to include various collaborative studies, including the Japan Collaborative Cohort, a collaborative research project conducted by six national medical research institutions in Japan, and the Asia Cohort Consortium, which involves more than one million Asian participants.

The cohort of the JPHC Study consisted of two cohorts, which had different starting dates; cohort I and cohort II. All subjects were registered residents aged 40-69 years who resided within 11 public health center areas nationwide from 1990 to 1994. The initial cohort, namely cohort I, was established in 1990 and enrolled residents of five public health centers (PHC) in Ninohe (Iwate), Yokote (Akita), Saku (Nagano), Chubu (Okinawa), and Katsushika (Tokyo). Cohort II was then established in 1993 in Mito (Ibaraki), Nagaoka (Niigata), Chuo-higashi (Kochi), Kamigoto (Nagasaki), Miyako (Okinawa) and Suita (Osaka). Apart from Tokyo and Osaka, the PHCs were not located in urban areas. Figure 2-1 depicts the geographic distribution and number of study participants in the study areas. A total of 140,420 residents enrolled in the JPHC Study. A notable difference between cohorts was age

distribution (40-59 years old for cohort I and 40-69 years old for cohort II). The sample from the Tokyo area was derived from participants of free health check-ups targeted at residents aged 40-50 years. These subjects might be more health conscious than participants from other areas.

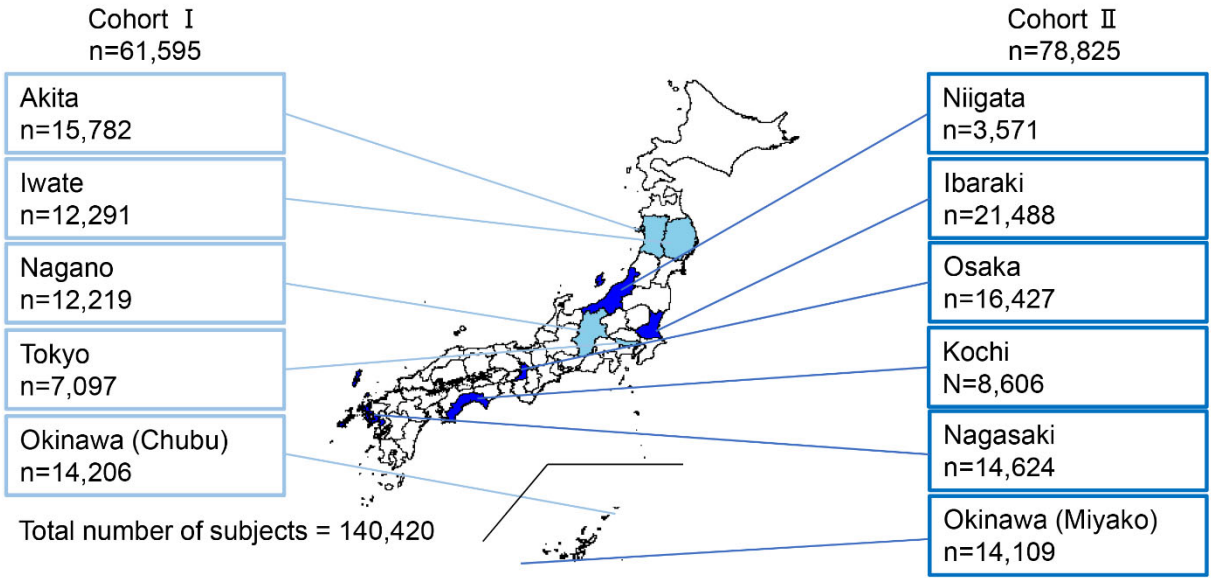


Figure 2-1: Map of Public Health Center areas and the number of participants in each PHC in the JPHC study

The survey consisted of the following three components: (1) a self-administered questionnaire survey, (2) blood sample collection, and (3) collection of health check-up data. The self-administered questionnaires at baseline were provided to all cohort subjects, permitting us to obtain comprehensive information on their (1) sociodemographic characteristics, (2) lifestyle, (3) family and personal medical history, (4) dietary habits, and (5) female reproductive history. Five-year and 10-year follow-up surveys were then distributed to participants to obtain additional information on individual dietary intake and change in anthropometric variables and lifestyle. Further details of the study design have been described elsewhere [91-97]. Ethical approval was obtained from the institutional review board of the National Cancer Center (approval number: 2001-021) and The University of Tokyo (approval number: 10508). The STROBE checklist was used to check items that should be included in the article [98].

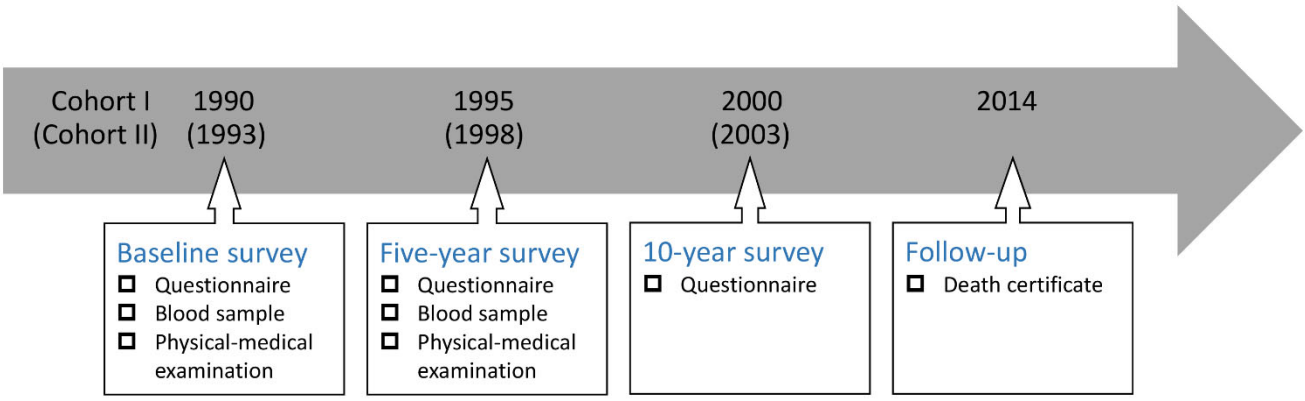


Figure 2-2: Study schedule for JPHC Study

2.1.2. Follow-up and identification of mortality

Survival or relocation of participants in the study was identified using municipal registries. Of subjects who returned basic questionnaires (n=59,983), 8,477 (14.1%) died, 35 (0.06%) emigrated outside of Japan, and 469 (0.8%) were lost to follow-up during the study period. Death certificates were collected through the local public health centers and used to confirm the cause of death with permission from the Ministry of Health, Labor and Welfare. Cause-specific mortality was assessed based on ICD-10. The major causes of death in Japanese women were used, namely cancer (C00–C97); heart disease (I20–I52) including ischaemic heart disease, pulmonary heart disease, disease of pulmonary circulation, and other forms of heart disease; cerebrovascular disease (I60–I69) including both haemorrhage and infarction; respiratory disease (J10–J18 and J40–J47) including seasonal influenza, pneumonia, and chronic lower respiratory diseases. Cancer was further divided into the most common subgroups among the cohort, including cancer of the lung (C34), stomach (C16), pancreatic (C25), breast (C50), and ovary (C56). Participants were followed from the baseline survey (1990, 1993) until death, last confirmation of survival for participants who relocated from the study area (i.e., migration), or end of follow-up (December 31, 2014), whichever occurred first. Subjects residing in the Katsushika and Suita public health center areas were scheduled to be followed for 20 years, until December 2009 and 2012, respectively, because the subjects from these areas frequently relocated (43.8% and 64.5%).

2.1.3. Study population

The JPHC Study consists of 140,420 participants (68,722 men and 71,698 women) who were registered residents in the registration system which included only Japanese nationals. Of the 71,698

women, those with non-Japanese nationality (n=20), pre-commencement emigration (n=86), incorrect birth date (n=5), duplicate registration (n=4) or a late report of migration before the start of the follow-up period (n=4,626) were excluded. Of these, 89.6% of women returned the completed questionnaire, leaving a total of 59,983 participants as eligible subjects. Because it is possible that foreigners were registered in this system due to marriage with a Japanese national, possible foreigners were identified by checking the response to the questionnaire.

2.1.4. Exclusion criteria

Women with a history of some diseases at the baseline survey may have changed their lifestyle. Doing so would introduce reverse causation and biased estimations when targeting lifestyle-related outcomes. Therefore, women with a history of diseases including cancer, heart disease, stroke, and surgical menopause at baseline survey (n=7,089) were excluded. In addition, subjects with at least one missing value of exposure variables and relevant covariates were also excluded in the complete-case analysis. These exclusions left 40,149 subjects in the analysis. The study schema is visually presented in Figures 2-3.

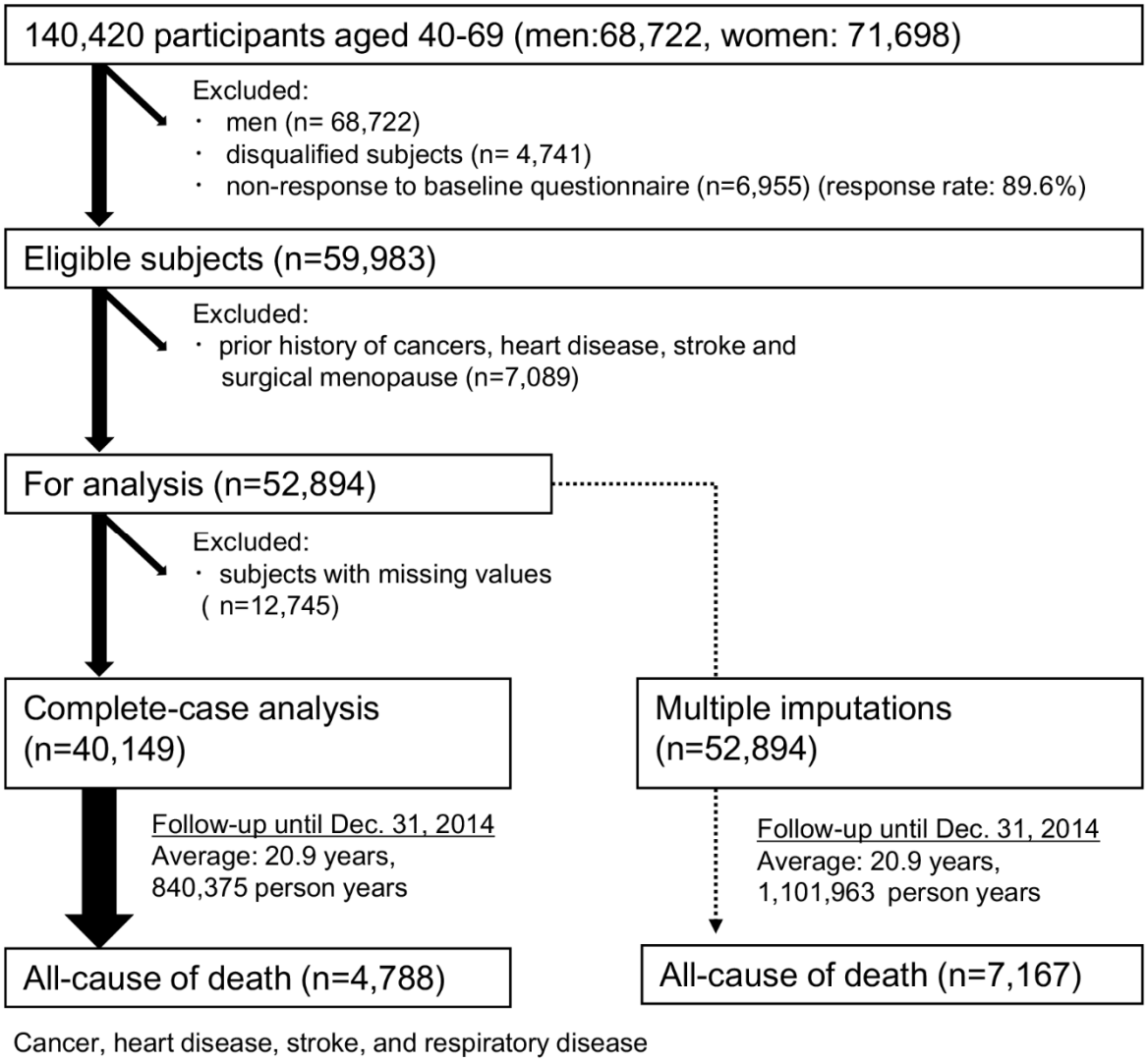


Figure 2-3: Study flow of the JPHC Study for all-cause and internal causes of death

2.1.5. Reproductive factors as exposure variables

Self-reported reproductive events captured at the baseline survey were selected by prior research [55, 99, 100]. Selected factors were categorized into binary, tertile or quartile groups based on the frequency distribution of variables within the cohort, as follows: parity, as the number of live birth or stillbirth, age at first birth, experience of breastfeeding, age at menarche, exogenous hormone use, length of menstrual cycle, menopausal status, age at menopause, and total fertility span. Details of categorization for exposure variables are shown in Table 2.1.

Two variables were made for parity, one to assess the effect of ever versus never parity, and the second to assess the dose-responsiveness of parity restricted to parous women. Specific details of the duration or frequency of breastfeeding were not available. Information on the use of any exogenous hormone was not asked about due to the limited use of these products in Japan at the time of the baseline survey [99], making it impossible to separate oral contraceptives from hormone replacement therapy. Subjects were asked if they still experience menstrual periods at the time of recruitment, or had entered either natural menopause or menopause due to a surgical procedure. Details of surgical procedures were not asked about. Menstrual status was then classified into pre-menopause, natural menopause, and surgical menopause. The question on age at menopause was restricted to post-menopausal women. Total fertility span was calculated as the interval between age at menarche and age at menopause (age at recruitment for pre-menopausal subjects). Calculation of the total number of ovulatory years was not possible due to a lack of data on the duration of pregnancy, breastfeeding and exogenous hormone use. Post-menopausal women were asked the average length of their menstrual

cycle before menopause.

After checking the data on reproductive factors, some unreliable values were identified. This may have been due to misreading of the question. If the time series of age at reproductive events was not realistic, values for these variables were categorized into the missing category. For example, although pregnancy should occur before menopause, or current age, some women reported first pregnancy after menopause or their current age. If nulliparous women responded with their age at first birth and breastfeeding, their age at first birth and breastfeeding was labeled as "nulliparous" within the categories. Although these participants could be grouped as parous women, the lack of data on the number of births prevented inclusion of these subjects in assessments involving the number of parity among parous women.

Table 2-1: Categorization of female reproductive factors

Variable	Category
Parity	Nulliparous, or parous
Number of birth (births)	(Nulliparous,) 1, 2, 3, 4 or 5
Age at first birth (years)	(Nulliparous,) ≤22, 23-24, 25-29, or ≥30
Breastfeeding	(Nulliparous,) no, or yes
Age at menarche (years)	≤13, 14, 15, or ≥16
Exogenous hormone use	Never, or ever
Length of menstrual cycle (days)	≤26, 27-29, or ≥30
Menopausal status	Pre, post, or surgical menopause
Age at menopause (years)	(Pre-menopause,) ≤46, 47-49, 50-51, or ≥52
Total fertility years (years)	≤28, 29-31, 32-34 or ≥35

2.1.6. Validity of reproductive factors

The validity of self-reported reproductive factors is listed in Table 2.2. In summary, most reproductive factors were highly accurate aside from age at menarche and length of menstrual cycle. The validity of recalled reproductive events tended to decrease with increasing number of years since the events [101].

Table 2-2: Validity of reproductive factors

Exposure variable	Level of validity	Author, year
Age at menarche	Moderate (k=0.35, r=0.66)	Cooper et al., 2006. Validity of age at menarche self-reported in adulthood. [101]
Length of menstrual cycle	Moderate (k=0.33)	Jukic et al., 2007. Accuracy of reporting of menstrual cycle lengths. [102]
Breastfeeding	High	Li et al., 2005. The validity and reliability of maternal recall of breastfeeding practice. [103]
Parity	High	Buka et al., 2004. The retrospective measurement of prenatal and perinatal events: accuracy of maternal recall. [104]
Age at first birth	High	Buka et al., 2004. The retrospective measurement of prenatal and perinatal events: accuracy of maternal recall. [104]
Hormone use	High	Hunter et al., 1997. Reproducibility of oral contraceptive histories and validity of hormone composition reported in a cohort of US women. [105]
Age at menopause	High	Tonkelaar et al., 1997. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. [106]

2.1.7. Other covariates

Potential confounders associated with mortality were selected based on prior research: body mass index (BMI, in kg/m^2) [14, 107]; smoking status [7, 108, 109]; alcohol consumption [8, 110]; living arrangement [111, 112]; history of disease (cancer, heart disease, stroke, hypertension, and diabetes); leisure-time sports or physical activity exercise [9, 10, 113]; job status [114]; total energy intake (kcal/d) [115]; and consumption of coffee and green tea [116, 117].

BMI was calculated by dividing weight (kg) by height (m^2) in the baseline survey. Regarding smoking status, participants were asked about their experience of smoking (never, or ever); and if they reported ever smoking, they were asked about their current smoking status and how many cigarettes they smoked per day. The participants selected habitual alcohol consumption as follows: hardly ever drink, 1-3 times per month, 1-2 times per week, 3-4 times per week, and almost every day. Regular drinkers, who drank more than one time per week, were asked about which types of alcohol and how much of each alcohol they consumed from the following: Japanese sake ("1 go", [a traditional Japanese unit of alcoholic drinks], 180ml, 23g of ethanol), shochu/awamori ("1 go", 180ml, 36g of ethanol), beer (large bottle 633ml, 23g of ethanol) , whiskey (1 glass 30ml, 13g of ethanol), wine (a glass 100ml, 6g of ethanol). Regarding living arrangement, participants were asked whether they lived with their spouse, child, parents, others, or alone. Living arrangement responses were categorized base on generations to avoid collinearity with another exposure variable (i.e., parity). Participants were asked about their frequency of physical activity as a closed question: seldom, 1-3 times per month, 1-2 times per week, 3-4 times per week, or almost every day. Consumption of coffee and green tea was selected

as follows: seldom, 1-2 times per week, 3-4 times per week, 1-2 cups per day, 3-4 cups per day, and more than 5 cups per day.

Table 2-3: Categorization of covariates according to outcomes

Variable	Category
Age (years)	≤44, 45-49, 50-54, 55-59, 60-64 or ≥65
PHC	11 areas
BMI (kg/m2)	<18.5, 18.5-24.9, 25-29.9 or ≥30
Smoking (per day)	Never, former, <20 cigarette or ≥20 cigarette
Alcohol consumption (per week)	No, <one time, 1–149g, 150–299g or ≥300g
Living arrangement	Alone, living with spouse or others without children, two generations, or three generations
History of disease	No, or yes
Physical activity (per week)	<1 time or ≥ 1 time
Job status	Employed or unemployed
Total energy intake (kcal per day)	<1000, 1000-1200 or ≤1200
Coffee consumption (per day)	Seldom, <1 cup or ≥1 cup
Tea consumption (per day)	Seldom, <1 cup or ≥1 cup
Perceived stress level	

2.1.8. Statistical analysis

Cox proportional hazards regression models were employed to estimate hazard ratios (HR) and 95% confidence intervals (CI) to assess the risk of death by all-cause and cause-specific mortality according to reproductive factors. Analyses were performed based on complete-case analysis, excluding subjects with at least one missing value for all variables of interest and possible confounders. Proportional hazard assumptions of age at recruitment, PHC, exposure variables, and confounders were verified using Schoenfeld residuals. Age was found to violate the proportional hazards assumption. Addressing the non-proportional hazard of age, age group was stratified in the models[118].

In the Cox proportional hazard model, it is assumed that the baseline hazard is common to all the individuals. However, for example, subjects aged 40 and 50 should have a different risk of dying (hazard). Suppose that there is a factor with K levels in a stratified Cox model, the hazard for an individual from age group stratum, say g, is

$$\lambda_g(t|Z(t)) = \lambda_{0g}(t)\exp\{\beta_0 Z(t)\},$$

where $\lambda_{0g}(t)$ is the baseline hazard for stratum g, g=1, …, K [119]. In the previous example, suppose stratum g=1 for age 40, and g=2 is age 50. The hazard ratio of risk of death is still e^{β} within each stratum while the baseline hazards for the two strata are different. Therefore, age was stratified instead

of being included as a predictor in the model. If the confounder is controlled using stratification, there is no way to estimate as summary relative risk. The proportional-hazards assumption was confirmed by the global test of Schoenfeld residual approach, and the model which was stratified by age category improved and held the proportional hazard assumption.

Study areas were further stratified in all models to allow for different baseline hazard due to the varying distribution of death rate across Japan [97]. A likelihood ratio test was conducted to confirm possible mediators between all reproductive factors and confounders.

The minimum model (Model A1) was built with stratification by age (≤44, 45-49, 50-54, 55-59, 60-64 or ≥65) and PHC (11). A multivariate-adjusted model (Model A2) was constructed based on Model A1 with additional adjustment for the possible confounders; body mass index (BMI, in kg/m^2; <18.5, 18.5 to 24.9, 25 to 29.9 or ≥30); smoking status (never, former, <20 cigarette/d or ≥20 cigarette/d); alcohol consumption (no, <1 time/w, 1–149g/w, 150–299g/w or ≥300g/w), leisure-time sports or physical activity exercise (<1 time/w or ≥ 1 time/w); consumption of coffee and green tea (almost never, <1 cup/d or ≥1 cup/d); total energy intake (kcal/d; <1000, 1000-1200 or ≤1200); job status (employed or unemployed); living arrangement (alone, living with spouse or others without children, two generations or three generations); history of hypertension (yes or no); and history of diabetes (yes or no). Because of many covariates, Spearman's correlation method (cut off: $|r|>0.3$) was used to identify

the strength of a correlation between paired data of reproductive factors [120], leaving parity (0, 1, 2, 3, 4 or ≥5), total fertility years (≤28, 29-31, 32-34, or ≥35 years), and exogenous hormone use for addition into the final models. Effects of *p*-values for linear trends were assessed for parity, age at first birth, age at menarche, length of menstrual cycle, age at menopause and total fertility years by assigning ordinal variables.

Additional sub analyses were conducted for different study populations based on complete-case analysis; analysis restricted to post-menopausal women, analysis restricted to non-smoking women, subjects stratified by BMI, and including surgically menopausal women. The reason for restricting subjects to postmenopausal women at recruitment is because hypoestrogenic status may accelerate the risk of mortality independent of age, and never-smoking women in order to rule out the effects of smoking. Considering causal links between potential confounders and reproductive factors, BMI was assessed as an intermediator of parity and all mortality by stratified analyses by BMI. A likelihood ratio test was conducted to compare models with and without multiplicative interaction terms and to calculate a *p*-value for statistical interaction. Because women with surgical menopause were not included in the model for all-cause and internal mortality, further analyses were conducted without the exclusion of surgically menopausal women (natural versus surgical menopause) to evaluate the effects of surgical menopause.

All *p*-values reported were two-sided, and $p < 0.05$ was set as the significance level. All analyses were performed with STATA version 14.0 software (StataCorp LP).

2.1.9. Multiple imputations as sensitivity analysis

One of the most common challenges in epidemiological research is handling missing values, which may result in varying inference. The most widely used approach to addressing missing data remains complete-case analysis, which may omit observed information by excluding subjects with non-available data on variables of interest. Many methodological studies which have compared approaches addressing missing data, and have concluded that this conventional approach may introduce potential selection bias and biased estimations depending on the pattern of missingness [121, 122].

Details of patterns of having missing data and possible limitations of each approach are described elsewhere [121]. Briefly, missingness of data is mainly categorized into three types: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). Data with MCAR is unrealistic in typical epidemiological research, and MAR is generally more likely than MNAR to be present in epidemiological studies [123]. MAR in a dataset occurs when the probability that a given subset of variables, for example, “pattern,” is observed depends only on the observed data. Given observed data alone, however, the mechanisms of MAR and MNAR are indistinguishable [123].

Generally, complete-case analysis could generate valid inferences under the assumption of MCAR [121]. Otherwise, this approach may yield biased estimations. In order to address these issues, the multiple imputations (MI) procedure was introduced by Rubin in 1986 [124]. The distribution of the observed data as posterior distribution is used to estimate a set of likely values of the data that are missing. This approach relies on specific modeling assumptions beyond assuming an ignorable nonresponse process.

Given that the missing-mechanism of variables in this study is not MCAR, the results obtained from the complete-case analysis may subject to potential selection bias and biased estimations. Addressing this challenge, the multiple imputations by chained equation (MICE) approach was performed as a sensitivity analysis. MICE is a flexible approach in which a series of regression models are performed wherein each variable with missing values is modeled conditional upon the other variables [123]. The basic statistics are included in the STATA software program and enable MICE to be performed using the *mi* procedure. The basic process is summarized in the following steps:

(1) In a set of variables, x_1, …, x_k, some or all of which have missing values. A simple imputation of all missing values in the dataset is performed at random using this distribution of observed data. These imputed values can be reset as missing again.

(2) A variable with a missing value, say x_1, is regressed as a dependent variable on other variables, x_2,

…,x_k which are complete data. Missing values in x_1 are then replaced by predictors derived from the posterior predictive distribution of x_1. The next variable with missing value, say x_k, is regressed on all other variables, including the imputed x_1, so that the imputed variable x_1 is used as an independent variable for the next regression model. Models can be selected by the type of dependent variable; for example, when the dependent variable is binary, logistic regression can be performed.

(3) The process is repeated for all variables with missing values in turn. The cycle in which all missing values are replaced with predictors is called an *iteration*. Although the procedure is usually repeated for ten iterations in order to stabilize the estimations, no criteria for the number of cycles has in fact been determined.

(4) Using completely imputed datasets, estimates are obtained using two steps: 1) running a standard analysis of each imputed dataset, and 2) combining the estimates from each dataset. The variance both within and between datasets reflects the uncertainty in the imputations.

Following these steps, all missing values of variables were imputed with 20 iterations, from expert opinion, using all covariates and auxiliary variables, including vital status, person-years, regularity of menstrual cycle, history of gynecological diseases, age at first pregnancy and number of pregnancies. Age, PHC, person-years, and mortality status had no missing value. Models were selected by the type of dependent variables which had at least one missing data; logistic regression for binary variables (i.e., parous versus nulliparous, history of diabetes), and an ordered logistic regression for the ordinal

variable (i.e., number of births, BMI). Cox proportional hazards models stratified by age category and PHC with adjustments for same covariates as complete-case analysis were conducted. Estimations were then combined using Rubin's rules [124]. Estimations were restricted to parous women for breastfeeding and age at first birth, and to post-menopausal women for age at menopause. Calculations for person-years and the number of cases across categories were a mean of estimations from all imputed datasets.

2.2. RESULTS

2.2.1. Characteristics of study subjects

After a mean follow-up of 20.9 years of 40,149 women (840,375 person-years), 4,788 total deaths were identified, including 1,838 deaths from cancer, 596 from heart disease, 504 from cerebrovascular disease and 254 from respiratory disease. Regarding site-specific cancer, 219 deaths from lung cancer, 212 from the stomach, 190 from pancreatic, 136 from the breast, and 61 from ovary were identified as well.

Table 2-4 shows the characteristics of the study population at baseline survey, and compares subjects with and without missing values, and before versus after menopause. Subjects without missing data were included in the complete-case analysis, and all eligible subjects were involved in the analysis using multiple imputations. 24% of eligible subjects had at least one missing datum, and were older and reported more menopause at baseline survey compared with subjects with complete data. Compared with pre-menopausal women, subjects with natural menopause were older, and reported more unemployment, less smoking, less alcohol consumption, more breastfeeding, older age at menarche, less usage of exogenous hormones, and more history of hypertension and diabetes.

This table also provides the percentage of death from all-cause and leading causes according to sample population. Subjects with missing values accounted for 24% of the total, while their mortality

was as high as 33%. This percentage discrepancy is thought to be caused by the aggregation of older subjects in the group with missing values. A notable discrepancy was seen in mortality from respiratory disease. 51.1% of deaths from the respiratory disease occurred in subjects with a missing value, and these were not included in the complete-case analyses. Looking at menopausal status, post-menopausal women had a high death rate compared to pre-menopausal women for all-cause and leading causes of death. In particular, death from respiratory disease occurred more in postmenopausal women.

Table 2-4: Basic characteristics of study subjects at baseline survey for analysis of all-cause and internal causes of death in the JPHC Study

Characteristic	Eligible subjects	*Among eligible subjects*			*Among eligible subjects with complete data*		
		Subjects with missing data	Subjects with complete data	*P*[a]	Pre-menopause	Post-menopause[b]	*P*[a]
Number of subjects (n)	52,894	12,745 (24.1%)	40,149（75.9%)		20,940 (51.5%)	19,751 (48.5%)	
Age at recruitment, y, mean (SD)	51.3 (8.1)	53.7(8.3)	50.6 (7.9)	<0.01	44.6 (3.9)	57.0 (5.7)	<0.01
BMI (kg/m^2) , mean (SD)	23.3 (3.2)	23.6 (3.3)	23.3 (3.1)	<0.01	23.0 (3.0)	23.5 (3.2)	<0.01
Total energy intake, Kcal, mean (SD)	1235.4 (295.9)	1196.1 (304.2)	1244.8 (292.8)	<0.01	1259.3 (292.7)	1230.3 (293.6)	<0.01
Employed, %	59.2	58.9	59.3	0.42	66.3	51.8	<0.01
Never smoker, %	90.8	90.7	90	0.36	88.7	93.1	<0.01
Regular drinker >1 d/wk, %	13.7	11.9	14.2	<0.01	18.3	9.8	<0.01
Physical activity >1 d/wk, %	18.5	18.1	18.7	<0.01	17.8	19.5	<0.01
Coffee intake >1 time/d, %	40.6	35.3	42.3	<0.01	53.8	29.8	<0.01
Green tea intake >1 time/d, %	74.6	73.8	74.9	<0.01	70	80.1	<0.01
Living in a three-generation family, %	23	20.4	23.8	<0.01	28.4	18.9	<0.01
History of hypertension, %	14.6	16.9	13.9	<0.01	6.9	21.3	<0.01
History of diabetes, %	2.7	3.1	2.6	0.03	1.4	3.9	<0.01
Reproductive factors							
Age at first pregnancy, y, mean (SD)[c]	24.3 (3.4)	24.1 (3.5)	24.4 (3.4)	0.57	24.5 (3.4)	24.3 (3.4)	0.57
Age at first birth, y, mean (SD) [c]	25.0 (3.5)	24.8 (3.6)	25.1 (3.5)	<0.01	25.2 (3.5)	24.9 (3.5)	<0.01
Number of births, mean (SD) [c,]	2.7 (1.5)	2.9 (1.8)	2.7 (1.5)	<0.01	2.4 (1.2)	2.9 (1.7)	<0.01
Age at menarche, y, mean (SD)	14.6 (1.9)	15.2 (2.1)	14.5 (1.8)	<0.01	13.7 (1.4)	15.2 (1.9)	<0.01
Age at menopause, y, , mean (SD)[b]	49.2 (3.5)	49.0 (3.8)	49.3 (3.4)	<0.01			
Total fertility span, y, mean (SD)	32.4 (4.2)	32.3 (4.3)	32.4 (4.1)	0.09	30.8 (3.7)	34.1 (3.9)	<0.01
Menstrual cycle, d, mean (SD)	27.7 (5.0)	27.5 (5.6)	27.8 (4.8)	<0.01	27.8 (4.3)	27.7 (5.3)	<0.01
Ever breastfed, %[c]	87	86.9	87	0.63	84.6	89.7	<0.01
Ever use of exogenous hormones, %	12.3	12.1	11.9	0.21	13.3	10.3	<0.01
Post-menopause at baseline, %	60.7	64.5	57	<0.01			

Characteristic	Eligible subjects	*Among eligible subjects*			*Among eligible subjects with complete data*		
		Subjects with missing data	Subjects with complete data	*P*[a]	Pre-menopause	Post-menopause[b]	*P*[a]
Outcome							
All-cause mortality, %	7,167	2,379 (33.2)	4,788 (66.8)		1,105 (30.0)	3,683 (70.0)	
Cancer, %	2,600	762 (29.3)	1,838 (70.7)		565 (30.7)	1,273 (69.3)	
Heart disease, %	979	383 (39.1)	596 (60.9)		85 (14.3)	511 (85.7)	
Stroke, %	771	267 (34.6)	504 (65.4)		106 (21.0)	398 (79.0)	
Respiratory disease, %	519	265 (51.1)	254 (48.9)		18 (7.1)	236 (92.9)	

BMI, body mass index; d, day; n, number; SD, standard deviation; wk, week; y, year

[a] Analysis of variance (ANOVA) for continuous variables or chi-square test for categorical variables

[b] Naturally menopausal women only

[c] Parous women only

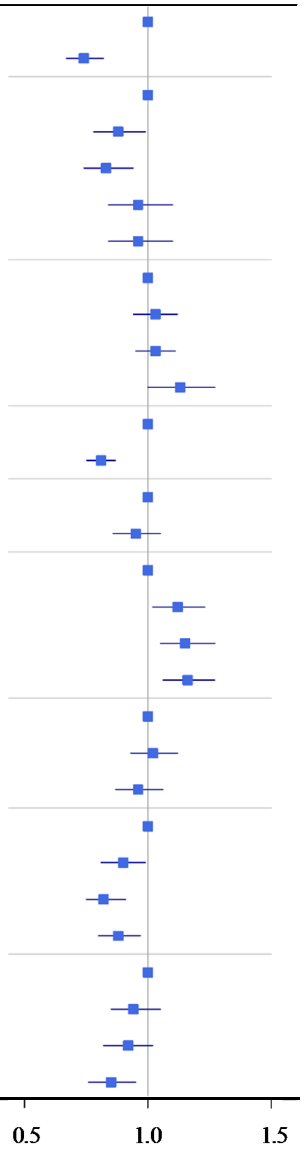
2.2.2. All-cause mortality

Table 2-5 presents adjusted HRs with 95% CIs of all-cause mortality according to reproductive factors. Parous was associated with a lower risk of all-cause mortality [0. 74 (95%CI: 0.67–0.82)]. Among parous women, an inverse association was found in women with two or three births compared with a single birth [2 births: 0.88 (95%CI: 0.78– 0.99); 3 births: 0.83 (95%CI: 0.74–0.94); P_{trend}: 0.59] and in women who had ever breastfed [0.81 (95%CI 0.75–0.87)]. A positive association was seen between later age at first birth (≥30 years) than the reference group (≤22 years) and all-cause mortality [≤22 years old: ≥30: 1.13, (95%CI: 1.00–1.27); P_{trend}: 0.11].

For menstrual variables, being older at menarche increased the risk across all categories [13 years old (reference); 14: 1.12 (95%CI: 1.02–1.23); 15: 1.15 (95%CI: 1.05–1.27); ≥16: HR, 1.16 (95% CI: 1.06–1.27); P_{trend}: <0.01]. Compared with women aged 46 years at menopause, older age at menopause was associated with a lower risk of mortality [47–49 years old: 0.90 (95%CI: 0.81–0.99); 50–51: 0.82 (95%CI: 0.75–0.91); ≥52: 0.88 (95%CI: 0.80 –0.97); P_{trend}: 0.01]. Overall, an inverse association between mortality risk and a longer fertility span was observed [≤28 years (reference); ≥35: 0.85 (95%CI: 0.76–0.95); P_{trend}: <0.01]. In contrast, no association was seen between all-cause mortality and length of menstrual cycle or exogenous hormone use.

Table 2-5: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality associated with reproductive factors in the JPHC Study by forest plot

Variables	Category	Person-years	Cases	Model A1[a] HR (95% CI)	*P*[c]	Model A2[b] HR (95% CI)	*P*[c]
Parous	No	55,540	447	1.00 (reference)		1.00 (reference)[d]	
	Yes	784,835	4,341	0.68 (0.62–0.75)		0.74 (0.67–0.82)	
Number of births[e]	1	61,453	372	1.00 (reference)	0.95	1.00 (reference)[d]	0.59
	2	304,845	1,366	0.81 (0.73–0.91)		0.88 (0.78–0.99)	
	3	240,528	1,151	0.75 (0.67–0.85)		0.83 (0.74–0.94)	
	4	98,185	684	0.88 (0.77–1.00)		0.96 (0.84–1.10)	
	≥5	79,825	768	0.90 (0.79–1.03)		0.96 (0.84–1.10)	
Age at first births, y[e]	≤22	169,506	1,063	1.00 (reference)	0.33	1.00 (reference)[d]	0.11
	23–24	211,752	1,168	0.99 (0.91,1.08)		1.03 (0.94–1.12)	
	25–29	330,040	1,695	0.99 (0.91–1.07)		1.03 (0.95–1.11)	
	≥30	73,537	415	1.11 (0.99–1.25)		1.13 (1.00–1.27)	
Breastfeeding[e]	Never	100,760	498	1.00 (reference)		1.00 (reference)[d]	
	Ever	677,809	3,843	0.75 (0.70–0.81)		0.81 (0.75–0.87)	
Exogenous hormone use	Never use	737,201	4,331	1.02 (0.93–1.12)		1.00 (reference)[f]	
	Ever use	103,174	457	0.97 (0.88–1.07)		0.96 (0.87–1.06)	
Age at menarche, y	≤13	262,546	871	1.00 (reference)	<0.01	1.00 (reference)[g]	<0.01
	14	210,725	1,024	1.12 (1.02–1.23)		1.12 (1.02–1.23)	
	15	170,911	1,054	1.15 (1.05–1.27)		1.15 (1.05–1.27)	
	≥16	196,193	1,836	1.16 (1.06–1.27)		1.16 (1.06–1.27)	
Menstrual cycle, d	≤26	139,189	633	1.00 (reference)	0.38	1.00 (reference)	0.27
	27–29	353,870	2,063	0.97 (0.88–1.07)		0.95 (0.86–1.05)	
	≥30	202,808	1,296	1.00 (reference)		1.00 (reference)	
Age at menopause, y[h]	≤46	65,314	649	1.00 (reference)	<0.01	1.00 (reference)[g]	0.01
	47–49	114,131	944	0.90 (0.81–0.99)		0.90 (0.81–0.99)	
	50–51	117,294	1,032	0.82 (0.74–0.90)		0.82 (0.75–0.91)	
	≥52	104,429	1,058	0.87 (0.79–0.96)		0.88 (0.80–0.97)	
Total fertility span, y[i]	≤28	179,946	635	1.00 (reference)	<0.01	1.00 (reference)[g]	<0.01
	29–31	169,803	803	0.94 (0.84–1.04)		0.94 (0.85–1.05)	
	32–34	201,737	1,314	0.90 (0.81–1.00)		0.92 (0.82–1.02)	
	≥35	288,889	2,036	0.84 (0.75–0.93)		0.85 (0.76–0.95)	



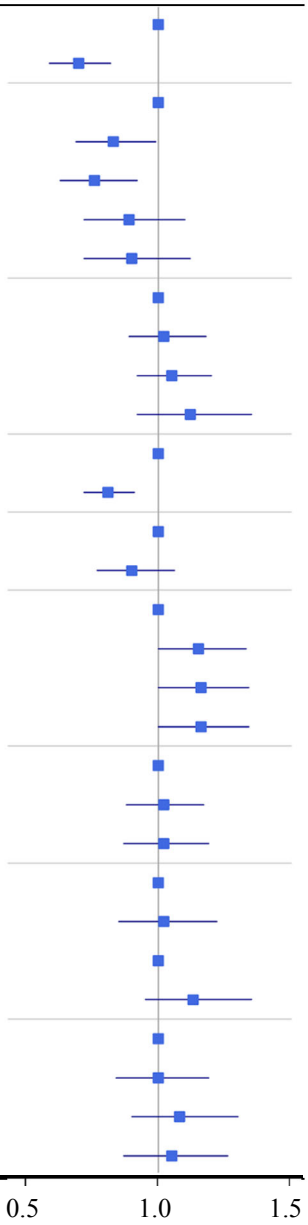
[a] Cox proportional hazards models stratified by age and public health center area
[b] Based on Model A1 and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, or ≥5); total fertility span; and exogenous hormones use
[c] *P* value for linear trend across categories of variable
[d] Adjustments as in footnote b except parity due to collinearity
[e] Parous women only
[f] Adjustments as in footnote b except exogenous hormones use due to collinearity
[g] Adjustments as in footnote b except total fertility span due to collinearity
[h] Naturally menopausal women only
[i] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.2.2. Total cancer

Regarding cancer mortality, a decreased risk was observed in women who gave birth [0. 70 (95%CI: 0.59–0.82)], had two or three births compared with a single birth [2 births: 0.83 (95%CI: 0.69–0.99); 3 births: 0.76 (95%CI: 0.63–0.92); P_{trend}: 0.79] and breastfed [0.81 (95%CI: 0.72–0.91)] (Table 2-6).

Table 2-6: Hazard ratios (HRs) and 95% confidence intervals (CIs) of total cancer associated with reproductive factors in the JPHC Study by forest plot

Variables	Category	Person–years	Cases	Model A2[a] HR (95% CI)	*P*[b]	Hazard ratio
Parous	No	55,540	175	1.00 (reference)[c]		
	Yes	784,835	1,663	0.70 (0.59–0.82)		
Number of births[d]	1	61,453	151	1.00 (reference)[c]	0.79	
	2	304,845	559	0.83 (0.69–0.99)		
	3	240,528	443	0.76 (0.63–0.92)		
	4	98,185	248	0.89 (0.72–1.10)		
	≥5	79,825	262	0.90 (0.72–1.12)		
Age at first births, y[d]	≤22	169,506	388	1.00 (reference)[c]	0.24	
	23–24	211,752	446	1.02 (0.89–1.18)		
	25–29	330,040	672	1.05 (0.92–1.20)		
	≥30	73,537	157	1.12 (0.92–1.35)		
Breastfeeding[d]	Never	100,760	199	1.00 (reference)[c]		
	Ever	677,809	1,464	0.81 (0.72–0.91)		
Exogenous hormone use	Never use	737,201	1,661	1.00 (reference)[e]		
	Ever use	103,174	177	0.90 (0.77–1.06)		
Age at menarche, y	≤13	262,546	377	1.00 (reference)[f]	0.08	
	14	210,725	424	1.15 (1.00–1.33)		
	15	170,911	404	1.16 (1.00–1.34)		
	≥16	196,193	633	1.16 (1.00–1.34)		
Menstrual cycle, d	≤26	139,189	255	1.00 (reference)	0.85	
	27–29	353,870	780	1.02 (0.88–1.17)		
	≥30	202,808	499	1.02 (0.87–1.19)		
Age at menopause, y[g]	≤46	65,314	191	1.00 (reference)[f]	0.17	
	47–49	114,131	324	1.02 (0.85–1.22)		
	50–51	117,294	369	1.00 (0.84–1.19)		
	≥52	104,429	389	1.13 (0.95–1.35)		
Total fertility span, y[h]	≤28	179,946	252	1.00 (reference)[f]		
	29–31	169,803	304	1.00 (0.84–1.19)	0.58	
	32–34	201,737	499	1.08 (0.90–1.30)		
	≥35	288,889	783	1.05 (0.87–1.26)		



[a] Cox proportional hazards models stratified by age and public health center area, and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, or ≥5); total fertility span; and exogenous hormones use

[b] *P* value for linear trend across categories of variable

[c] Adjustments as in footnote a except parity due to collinearity

[d] Parous women only

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

[f] Adjustments as in footnote a except total fertility span due to collinearity

[g] Naturally menopausal women only

[h] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.1.4. Site-specific cancer

Figure 2-4, and Tables 2-7 and 2-8 present the results for site-specific analyses of cancer mortality. A suggestive increased risk of lung cancer with late age at menarche was found [P_{trend}: 0.08]. Regarding stomach cancer, women with ever breastfeeding [0.69 (95%CI: 0.50–0.96)] and exogenous hormone use [0.55 (95%CI: 0.31–0.98)] had a lower risk from mortality. Compared to those at the earliest age at menarche, women aged 14 years or older than 16 years at menarche showed an increased risk of stomach cancer death, although a clear trend was not observed [13 years old (reference); 14: 1.81 (95%CI: 1.20–2.72); 15: 1.11 (95%CI: 0.69–1.78); ≥16: HR, 1.69 (95% CI: 1.09–2.63); P_{trend}: 0.14]. No statistically significant association was found in mortality risk from pancreatic cancer.

Mortality from breast and ovarian cancers was more sensitive to reproductive factors. Ever parity was associated with a 67% decrease in risk of death by breast cancer compared to nulliparous women [0.33 (95%CI: 0.20–0.54)]. A clear decreasing trend in breast cancer risk was seen with increasing parity [1 birth (reference); 2 births: 0.42 (95%CI: 0.25–0.70); 3 births: 0.32 (95%CI: 0.18–0.56); 4 births: 0.39 (95%CI: 0.19–0.80); ≥5 births: 0.28 (95%CI: 0.11–0.71);P_{trend}: <0.01] and age at first birth [≤22 years old (reference): ≥30: 3.60, (95%CI: 1.95–6.65); P_{trend}: <0.01]. A decreased mortality risk from ovarian cancer was seen in ever parity [0.36 (95%CI: 0.18–0.75)] and breastfeeding [0.47 (95%CI: 0.27-0.82)]. High parity was inversely associated with risk of ovarian cancer, but the number of events in the high parity group was small [1 birth (reference); ≥5 births: 0.01 (95%CI: 0.11–0.87); P_{trend}: <0.08].

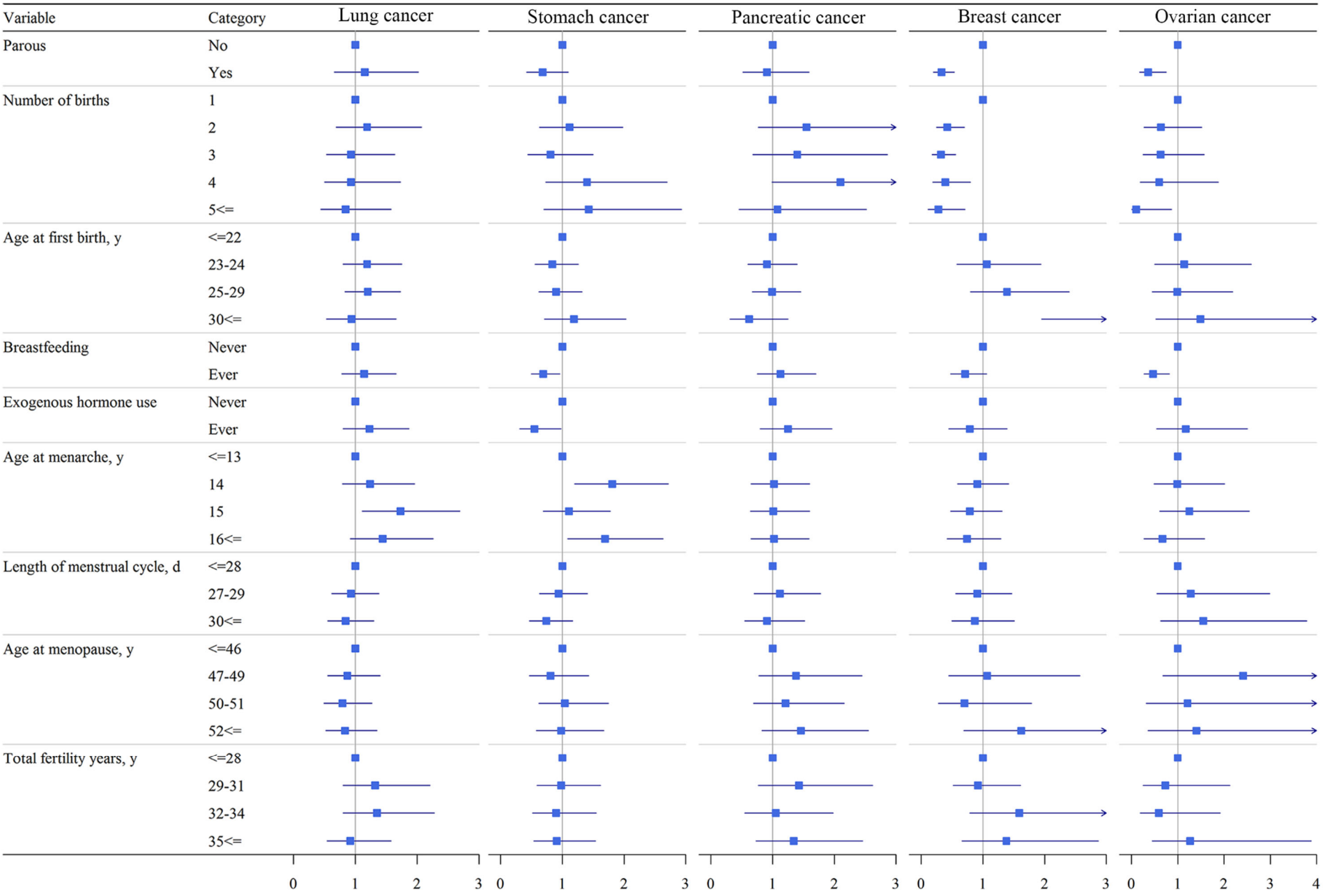


Figure 2-4: Hazard ratios (HRs) and 95% confidence intervals (CIs) of site-specific cancer and reproductive factors in the JPHC Study

Table 2-7: Hazard ratios (HRs) and 95% confidence intervals (CIs) of major and reproductive-related cancers according to reproduction-related factors and hormone use in the JPHC Study

Variables	Person–years	Lung cancer (C34)		Stomach cancer (C16)		Pancreatic cancer (C25)		Breast cancer (C50)		Ovary cancer (C56)	
		Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
Parous											
No	26,323	14	1.00 (reference)[b]	19	1.00 (reference)[b]	14	1.00 (reference)[b]	21	1.00 (reference)[b]	11	1.00 (reference)[b]
Yes	374,846	205	1.15 (0.66–2.02)	193	0.68 (0.42–1.10)	176	0.91 (0.52–1.59)	115	0.33 (0.20–0.54)	50	0.36 (0.18–0.75)
Number of births[c]											
1	28,357	16	1.00 (reference)[b]	14	1.00 (reference)[b]	9	1.00 (reference)[b]	22	1.00 (reference)[b]	7	1.00 (reference)[b]
2	121,756	69	1.19 (0.69–2.07)	78	1.12 (0.63–1.98)	62	1.55 (0.77–3.12)	46	0.42 (0.25–0.70)	21	0.64 (0.27–1.52)
3	109,934	53	0.93 (0.53–1.64)	44	0.81 (0.44–1.50)	51	1.40 (0.68–2.86)	26	0.32 (0.18–0.56)	15	0.63 (0.25–1.57)
4	55,685	31	0.93 (0.50–1.73)	31	1.40 (0.73–2.70)	36	2.10 (0.99–4.44)	13	0.39 (0.19–0.80)	6	0.60 (0.19–1.88)
≥5	59,115	36	0.84 (0.44–1.58)	26	1.43 (0.70–2.93)	18	1.08 (0.46–2.52)	8	0.28 (0.11–0.71)	1	0.10 (0.01–0.87)
P[d]			0.24		0.37		0.71		<0.01		0.08
Age at first birth, y[c]											
≤22	88,293	49	1.00 (reference)[b]	46	1.00 (reference)[b]	44	1.00 (reference)[b]	19	1.00 (reference)[b]	10	1.00 (reference)[b]
23–24	98,475	56	1.19 (0.80–1.75)	49	0.84 (0.56–1.26)	46	0.91 (0.60–1.40)	25	1.06 (0.58–1.94)	15	1.14 (0.50–2.59)
25–29	153,622	84	1.20 (0.83–1.73)	77	0.90 (0.62–1.32)	76	0.99 (0.67–1.46)	46	1.39 (0.80–2.40)	19	0.99 (0.45–2.19)
≥30	34,455	16	0.94 (0.53–1.66)	21	1.19 (0.71–2.03)	10	0.62 (0.31–1.25)	25	3.60 (1.95–6.65)	6	1.49 (0.53–4.23)
P[d]			0.73		0.76		0.47		<0.01		0.71
Breastfeeding[c]											
Never	64,283	34	1.00 (reference)[b]	30	1.00 (reference)[b]	14	1.00 (reference)[b]	13	1.00 (reference)[b]	10	1.00 (reference)[b]
Ever	333,547	183	1.14 (0.78–1.66)	161	0.69 (0.50–0.96)	161	1.13 (0.75–1.70)	101	0.71 (0.48–1.06)	40	0.47 (0.27–0.82)
Exogenous hormone use											
Never use	357,757	196	1.00 (reference)[e]	199	1.00 (reference)[e]	166	1.00 (reference)[e]	122	1.00 (reference)[e]	53	1.00 (reference)[e]
Ever use	43,411	26	1.23 (0.80–1.87)	13	0.55 (0.31–0.98)	24	1.25 (0.80–1.96)	14	0.79 (0.45–1.39)	8	1.17 (0.54–2.51)

[a]Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use

[b]Adjustments as in footnote a except parity due to collinearity

[c] Parous women only

[d]*P* value for linear trend across categories of variable

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

Table 2-8: Hazard ratios (HRs) and 95% confidence intervals (CIs) of major and reproductive-related cancers according to menstruation-related factors in the JPHC Study

Variables	Person–years	Lung cancer (C34)		Stomach cancer (C16)		Pancreatic cancer (C25)		Breast cancer (C50)		Ovary cancer (C56)	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Age at menarche, y											
≤13	68,756	35	1.00 (reference)[b]	39	1.00 (reference)[b]	38	1.00 (reference)[b]	48	1.00 (reference)[b]	18	1.00 (reference)[b]
14	82,566	43	1.24 (0.79–1.96)	64	1.81 (1.20–2.72)	42	1.02 (0.65–1.60)	36	0.91 (0.59–1.42)	15	0.99 (0.49–2.01)
15	92,957	58	1.73 (1.11–2.69)	36	1.11 (0.69–1.78)	42	1.01 (0.64–1.60)	25	0.79 (0.48–1.31)	17	1.25 (0.61–2.55)
≥16	156,890	83	1.44 (0.92–2.26)	73	1.69 (1.09–2.63)	68	1.02 (0.65–1.59)	27	0.74 (0.42–1.29)	11	0.67 (0.27–1.58)
P[c]			0.08		0.14		0.95		0.24		0.58
Menstrual cycle, d											
≤26	49,928	34	1.00 (reference)	34	1.00 (reference)	24	1.00 (reference)	24	1.00 (reference)	7	1.00 (reference)
27–29	180,559	96	0.93 (0.62–1.38)	90	0.94 (0.63–1.41)	85	1.12 (0.70–1.78)	53	0.91 (0.56–1.47)	25	1.28 (0.55–2.99)
≥30	105,624	58	0.84 (0.55–1.30)	47	0.74 (0.47–1.17)	45	0.91 (0.55–1.52)	29	0.87 (0.50–1.51)	17	1.55 (0.63–3.79)
P[c]			0.43		0.17		0.55		0.64		0.33
Age at menopause, y[d]											
≤46	65,314	31	1.00 (reference)[b]	23	1.00 (reference)[b]	17	1.00 (reference)[b]	8	1.00 (reference)[b]	3	1.00 (reference)[b]
47–49	114,131	44	0.87 (0.55–1.40)	31	0.81 (0.47–1.43)	39	1.38 (0.78–2.45)	15	1.07 (0.45–2.57)	14	2.41 (0.68–8.47)
50–51	117,294	42	0.79 (0.49–1.27)	47	1.04 (0.62–1.75)	42	1.21 (0.69–2.16)	11	0.70 (0.28–1.79)	8	1.21 (0.32–4.60)
≥52	104,429	42	0.83 (0.52–1.35)	40	0.98 (0.58–1.67)	48	1.46 (0.83–2.55)	20	1.62 (0.69–3.80)	8	1.40 (0.36–5.36)
P[c]			0.44		0.74		0.31		0.30		0.72
Total fertility span, y[e]											
≤28	30,489	26	1.00 (reference)[b]	32	1.00 (reference)[b]	17	1.00 (reference)[b]	31	1.00 (reference)[b]	8	1.00 (reference)[b]
29–31	53,171	46	1.32 (0.80–2.21)	37	0.98 (0.59–1.62)	34	1.43 (0.77–2.62)	25	0.92 (0.52–1.61)	8	0.73 (0.25–2.13)
32–34	115,002	71	1.35 (0.80–2.28)	53	0.90 (0.52–1.55)	44	1.05 (0.55–1.98)	38	1.59 (0.79–3.19)	11	0.59 (0.19–1.92)
≥35	202,506	76	0.92 (0.54–1.58)	90	0.91 (0.54–1.54)	95	1.34 (0.73–2.46)	42	1.38 (0.66–2.87)	34	1.27 (0.45–3.88)
P[c]			0.30		0.71		0.48		0.37		0.25

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use

[b] Adjustments as in footnote a except the total fertility span due to collinearity

[c] *P* value for linear trend across categories of variable

[d] Naturally menopausal women only

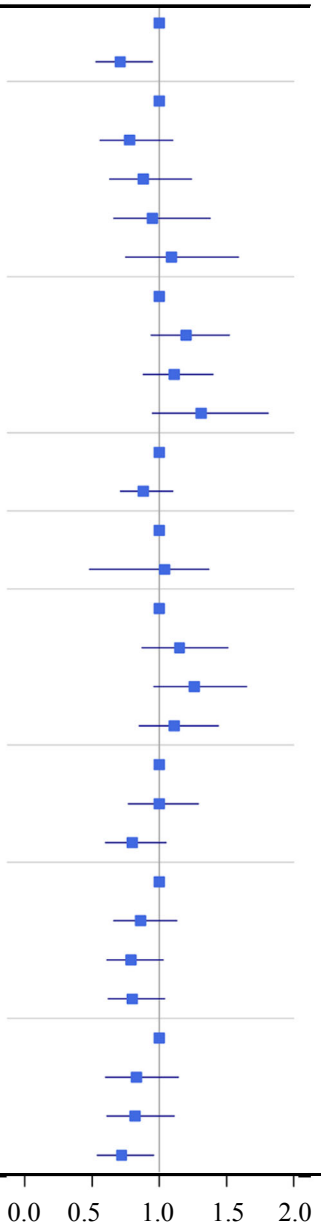
[e] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.1.5. Heart disease

Risk of mortality from heart disease was lower in parous women [0.71 (95%CI: 0.53–0.95] and women with a longer fertility span [≤28 years (reference); ≥35: 0.72 (95%CI 0.54–0.96); P_{trend}: 0.02] (Table 2-9). A potential decreased risk from heart disease was seen in late age at menopause [≤ 46 years old (reference); 50–51: 0.79 (95%CI: 0.61–1.03); ≥52: 0.80 (95%CI 0.62–1.04); P_{trend}: 0.10], and long length of menstrual cycle [P_{trend}: 0.06].

Table 2-9: Hazard ratios (HRs) and 95% confidence intervals (CIs) of heart disease associated with reproductive factors in the JPHC Study by forest plot

Variables	Category	Person-years	Cases	Model A2[a] HR (95% CI)	P[b]	Hazard ratio
Parous	No	55,540	55	1.00 (reference)[c]		
	Yes	784,835	541	0.71 (0.53–0.95)		
Number of births[d]	1	61,453	55	1.00 (reference)[c]	0.14	
	2	304,845	45	0.78 (0.56–1.10)		
	3	240,528	142	0.88 (0.63–1.24)		
	4	98,185	149	0.95 (0.66–1.38)		
	≥5	79,825	87	1.09 (0.75–1.59)		
Age at first births, y[d]	≤22	169,506	129	1.00 (reference)[c]	0.21	
	23–24	211,752	153	1.20 (0.94–1.52)		
	25–29	330,040	205	1.11 (0.88–1.40)		
	≥30	73,537	54	1.31 (0.95–1.81)		
Breastfeeding[d]	Never	100,760	47	1.00 (reference)[c]		
	Ever	677,809	494	0.88 (0.71–1.10)		
Exogenous hormone use	Never use	737,201	538	1.00 (reference)[e]		
	Ever use	103,174	58	1.04 (0.48–1.37)		
Age at menarche, y	≤13	262,546	89	1.00 (reference)[f]	0.56	
	14	210,725	122	1.15 (0.87–1.51)		
	15	170,911	142	1.26 (0.96–1.65)		
	≥16	196,193	243	1.11 (0.85–1.44)		
Menstrual cycle, d	≤26	139,189	81	1.00 (reference)	0.06	
	27–29	353,870	276	1.00 (0.77–1.29)		
	≥30	202,808	154	0.80 (0.60–1.05)		
Age at menopause, y[g]	≤46	65,314	94	1.00 (reference)[f]	0.10	
	47–49	114,131	131	0.86 (0.66–1.13)		
	50–51	117,294	147	0.79 (0.61–1.03)		
	≥52	104,429	146	0.80 (0.62–1.04)		
Total fertility span, y[h]	≤28	179,946	73	1.00 (reference)[f]		
	29–31	169,803	91	0.83 (0.60–1.14)	0.02	
	32–34	201,737	167	0.82 (0.61–1.11)		
	≥35	288,889	265	0.72 (0.54–0.96)		



[a] Cox proportional hazards models stratified by age and public health center area, and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, or ≥5); total fertility span; and exogenous hormones use

[b] P value for linear trend across categories of variable

[c] Adjustments as in footnote a except parity due to collinearity

[d] Parous women only

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

[f] Adjustments as in footnote a except total fertility span due to collinearity

[g] Naturally menopausal women only

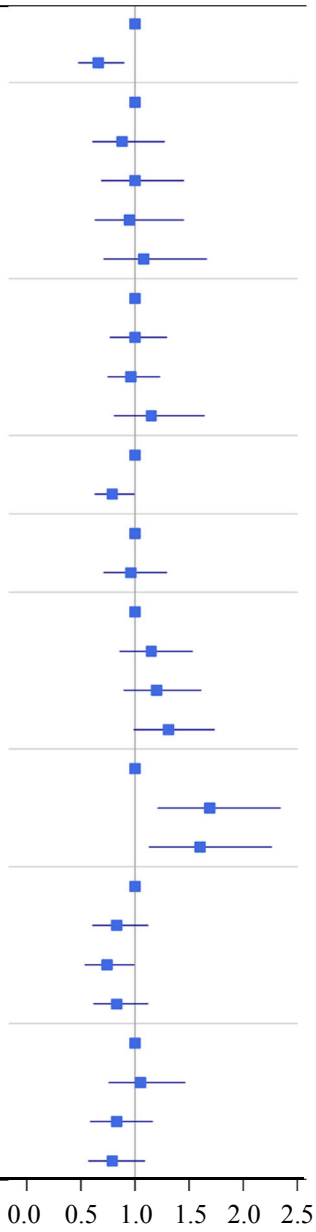
[h] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.1.6. Cerebrovascular disease

An inverse association with mortality from cerebrovascular disease was observed in parous women [0.66 (95%CI: 0.48–0.90)] and women who breastfed [0.79 (95%CI: 0.63–0.99)] (Table 2-10). Women with a longer fertility span had a trend of decreased risk of cerebrovascular disease mortality, but point estimates were not significant [P_{trend}: 0.04]. The longer menstrual cycle [≤26 days (reference); 27–29: 1.69 (95%CI: 1.21–2.34); ≥30: 1.60 (95%CI: 1.13–2.26); P_{trend}: 0.04] was associated with an increased risk of mortality from cerebrovascular disease. A suggestive positive association between cerebrovascular disease risk and late age at menarche was seen [13 years old (reference); ≥16: HR, 1.31 (95% CI: 0.99–1.73); P_{trend}: 0.07].

Table 2-10: Hazard ratios (HRs) and 95% confidence intervals (CIs) of cerebrovascular disease associated with reproductive factors in the JPHC Study by forest plot

Variables	Category	Person-years	Cases	Model A2[a] HR (95% CI)	P[b]	Hazard ratio
Parous	No	55,540	49	1.00 (reference)[c]		
	Yes	784,835	455	0.66 (0.48–0.90)		
Number of births[d]	1	61,453	37	1.00 (reference)[c]	0.40	
	2	304,845	137	0.88 (0.61–1.27)		
	3	240,528	139	1.00 (0.69–1.45)		
	4	98,185	65	0.95 (0.63–1.45)		
	≥5	79,825	77	1.08 (0.71–1.66)		
Age at first births, y[d]	≤22	169,506	117	1.00 (reference)[c]	0.77	
	23–24	211,752	122	1.00 (0.77–1.29)		
	25–29	330,040	171	0.96 (0.75–1.23)		
	≥30	73,537	45	1.15 (0.81–1.64)		
Breastfeeding[d]	Never	100,760	50	1.00 (reference)[c]		
	Ever	677,809	405	0.79 (0.63–0.99)		
Exogenous hormone use	Never use	737,201	452	1.00 (reference)[e]		
	Ever use	103,174	52	0.96 (0.71–1.29)		
Age at menarche, y	≤13	262,546	85	1.00 (reference)[f]	0.07	
	14	210,725	106	1.15 (0.86–1.53)		
	15	170,911	112	1.20 (0.90–1.61)		
	≥16	196,193	201	1.31 (0.99–1.73)		
Menstrual cycle, d	≤26	139,189	44	1.00 (reference)	0.04	
	27–29	353,870	230	1.69 (1.21–2.34)		
	≥30	202,808	141	1.60 (1.13–2.26)		
Age at menopause, y[g]	≤46	65,314	75	1.00 (reference)[f]	0.24	
	47–49	114,131	101	0.83 (0.61–1.12)		
	50–51	117,294	105	0.74 (0.54–0.99)		
	≥52	104,429	117	0.83 (0.62–1.12)		
Total fertility span, y[h]	≤28	179,946	65	1.00 (reference)[f]	0.04	
	29–31	169,803	97	1.05 (0.76–1.46)		
	32–34	201,737	132	0.83 (0.59–1.16)		
	≥35	288,889	210	0.79 (0.57–1.09)		



[a] Cox proportional hazards models stratified by age and public health center area, and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, or ≥5); total fertility span; and exogenous hormones use

[b] P value for linear trend across categories of variable

[c] Adjustments as in footnote a except parity due to collinearity

[d] Parous women only

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

[f] Adjustments as in footnote a except total fertility span due to collinearity

[g] Naturally menopausal women only

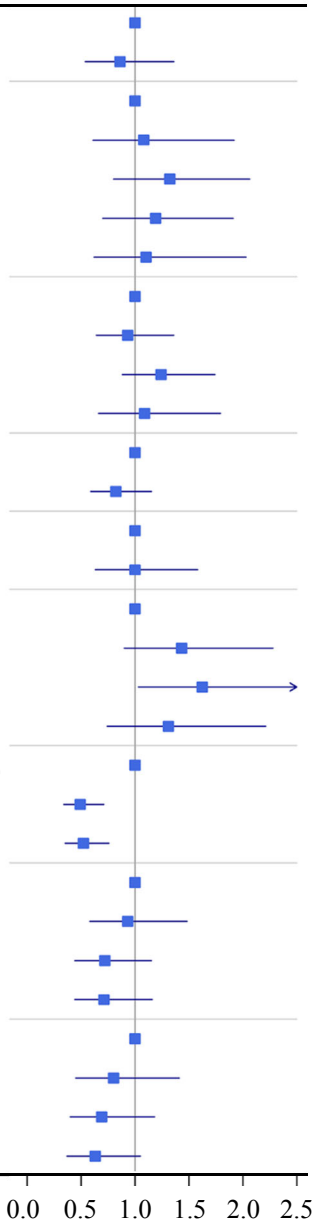
[h] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.1.7. Respiratory disease

An inverse trend of mortality risk from respiratory disease was found among women with a long length of menstrual cycle [≤26 days (reference); 27–29: 0.49 (95%CI: 0.34–0.71); ≥30: 0.52 (95%CI: 0.35–0.76); P_{trend}: <0.01], late age at menopause [P_{trend}: 0.04], and long fertility period [P_{trend}: 0.01] (Table 2-11). Compared to youngest age group at menarche, only 15 years age at menarche was associated with increased risk of respiratory disease, but there was no significant linear trend with increasing age at onset [13 years old (reference); 15: HR, 1.62 (95% CI: 1.03–2.55); P_{trend}: 0.49].

Table 2-11: Hazard ratios (HRs) and 95% confidence intervals (CIs) of respiratory disease associated with reproductive factors in the JPHC Study by forest plot

Variables	Category	Person-years	Cases	Model A2[a] HR (95% CI)	*P*[b]	Hazard ratio
Parous	No	55,540	21	1.00 (reference)[c]		
	Yes	784,835	233	0.86 (0.54-1.36)		
Number of births[d]	1	61,453	15	1.00 (reference)[c]	0.69	
	2	304,845	57	1.08 (0.61-1.92)		
	3	240,528	74	1.32 (0.80-2.06)		
	4	98,185	40	1.19 (0.70-1.91)		
	≥5	79,825	47	1.10 (0.62-2.03)		
Age at first births, y[d]	≤22	169,506	58	1.00 (reference)[c]	0.26	
	23-24	211,752	53	0.93 (0.64-1.36)		
	25-29	330,040	100	1.24 (0.88-1.74)		
	≥30	73,537	22	1.09 (0.66-1.79)		
Breastfeeding[d]	Never	100,760	24	1.00 (reference)[c]		
	Ever	677,809	209	0.82 (0.59-1.15)		
Exogenous hormone use	Never use	737,201	233	1.00 (reference)[e]		
	Ever use	103,174	21	1.00 (0.63-1.58)		
Age at menarche, y	≤13	262,546	28	1.00 (reference)[f]	0.49	
	14	210,725	50	1.43 (0.90-2.28)		
	15	170,911	63	1.62 (1.03-2.55)		
	≥16	196,193	113	1.31 (0.74-2.21)		
Menstrual cycle, d	≤26	139,189	47	1.00 (reference)	<0.01	
	27-29	353,870	90	0.49 (0.34-0.71)		
	≥30	202,808	68	0.52 (0.35-0.76)		
Age at menopause, y[g]	≤46	65,314	45	1.00 (reference)[f]	0.04	
	47-49	114,131	65	0.93 (0.58-1.48)		
	50-51	117,294	65	0.72 (0.44-1.15)		
	≥52	104,429	61	0.71 (0.44-1.16)		
Total fertility span, y[h]	≤28	179,946	33	1.00 (reference)[f]	0.01	
	29-31	169,803	39	0.80 (0.45-1.41)		
	32-34	201,737	75	0.69 (0.40-1.18)		
	≥35	288,889	107	0.63 (0.37-1.05)		



[a] Cox proportional hazards models stratified by age and public health center area, and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, or ≥5); total fertility span; and exogenous hormones use

[b] *P* value for linear trend across categories of variable

[c] Adjustments as in footnote a except parity due to collinearity

[d] Parous women only

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

[f] Adjustments as in footnote a except total fertility span due to collinearity

[g] Naturally menopausal women only

[h] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.1.8. Secondary analyses and sensitivity analysis

When subjects were classified by BMI, mean parity in women with BMI<25Kg/m^2 and BMI≥25Kg/m^2 group was 2.5 and 2.9 births, respectively (Table 2-12). Although the magnitude of and trend in parity-related mortality differed by BMI group, tests for interaction showed insignificant results (P_{int}=0.18 for all-cause mortality). The model without BMI yielded few changes in estimation (less than 5%).

Table 2-12: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with parity after stratifying by BMI in the JPHC Study

Cause of death	BMI category	BMI < 25kg/m^2					BMI ≥ 25kg/m^2					P_{int}[c]
	Parity	0	1–2	3–4	≥5		0	1–2	3–4	≥5		
	Person-years	43,522	287,499	243,097	47,877	P_{trend}[b]	12,018	78,798	95,616	31,947	P_{trend}[b]	
All-cause mortality	Cases	335	1,275	1,234	462		112	463	601	306		
	HR[a]	1.00	0.67	0.63	0.70	<0.01	1.00	0.84	0.84	0.87	0.51	0.18
	95% CI[a]	reference	0.60–0.76	0.63–0.71	0.60–0.82		reference	0.68–1.04	0.68–1.04	0.69–1.10		
Cancer	Cases	134	525	457	158		41	185	234	104		
	HR[a]	1.00	0.65	0.59	0.70	<0.01	1.00	0.87	0.86	0.81	0.34	0.30
	95% CI[a]	reference	0.53–0.79	0.48–0.71	0.55–0.90		reference	0.61–1.24	0.61–1.21	0.55–1.18		
Heart disease	Cases	40	134	167	79		15	53	69	39		
	HR[a]	1.00	0.56	0.64	0.83	0.78	1.00	0.80	0.81	0.84	0.77	0.48
	95% CI[a]	reference	0.39–0.81	0.45–0.91	0.55–1.26		reference	0.44–1.47	0.45–1.47	0.44–1.60		
Cerebrovascular disease	Cases	40	123	137	41		9	51	67	36		
	HR[a]	1.00	0.50	0.56	0.58	0.18	1.00	0.90	0.95	1.24	0.35	0.20
	95% CI[a]	reference	0.35–0.73	0.39–0.82	0.36–0.93		reference	0.43–1.87	0.47–1.96	0.57–2.69		
Respiratory disease	Cases	16	52	83	34		5	20	31	13		
	HR[a]	1.00	0.66	0.86	0.84	0.71	1.00	0.73	0.82	0.55	0.39	0.45
	95% CI[a]	reference	0.37–1.18	0.49–1.49	0.45–1.59		reference	0.26–2.07	0.30–2.22	0.18–1.64		

BMI, Body mass index

[a] Cox proportional hazards models stratified by age at recruitment and study area and adjusted for smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; total fertility span; and exogenous hormone use

[b] *P* value for linear trend across categories of variable

[c] *P* value for likelihood ratio test

The results for natural versus surgical menopause are shown in Table 2-13. A substantial risk reduction in mortality from respiratory disease [0.59 (95%CI: 0.37–0.97)], and marginally reduced mortality risk from all-cause [0.94 (95%CI: 0.85–1.03)], heart disease [0.78 (95%CI: 0.59–1.04)], and cerebrovascular disease [0.73 (95%CI: 0.53–1.01)] was also found among women who had surgical menopause.

Table 2-13: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with menopausal type in the JPHC Study

Variable	Person-years	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Menopausal type[b]											
Natural menopause	401,168	3,683	1.00 (reference)	1,273	1.00 (reference)	518	1.00 (reference)	398	1.00 (reference)	236	1.00 (reference)
Surgical menopause	75,989	495	0.94 (0.85–1.03)	203	1.06 (0.91–1.24)	56	0.78 (0.59–1.04)	45	0.73 (0.53–1.01)	18	0.59 (0.37–0.97)

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use

[b] Both natural and surgical menopausal women

Figure 2-5 compares the results from the main analysis, secondary analyses and multiply imputed datasets for all-cause mortality. When we restricted analyses to subjects with natural menopause (Tables 2-14 and 2-15) and those who had never smoked (Tables 2-16 and 2-17) for all-cause and internal causes of death, similar results were observed. Among naturally post-menopausal women, however, the inverse association of all-cause mortality with age at first birth, cancer mortality with two or three births, and heart disease mortality with parous became marginal. Similar associations remained among never-smokers, except for cerebrovascular disease. The significant association between mortality risk from cerebrovascular disease and increasing parity, ever breastfeeding, long length of menstrual cycle, and long fertility years altered toward null.

Compared to the complete-case analyses, results obtained using multiply imputed datasets show narrow confidence intervals, possibly due to increased sample size and number of cases (Tables 2-18 and 2-19). Some associations between mortality and reproductive factors became stronger, as follows: all-cause mortality and increasing parity and late age at first birth; cancer mortality and increasing parity; heart disease and parous versus nulliparous, late age at menopause, and long fertility years; and cerebrovascular disease and long fertility years. Associations that weakened or altered to null included mortality from cancer and breastfeeding; cerebrovascular disease and increasing parity, breastfeeding and long length of menstrual cycle; and respiratory disease and long length of menstrual cycle. Although some marginal associations became null or significant, overall magnitude and direction did not substantially change.

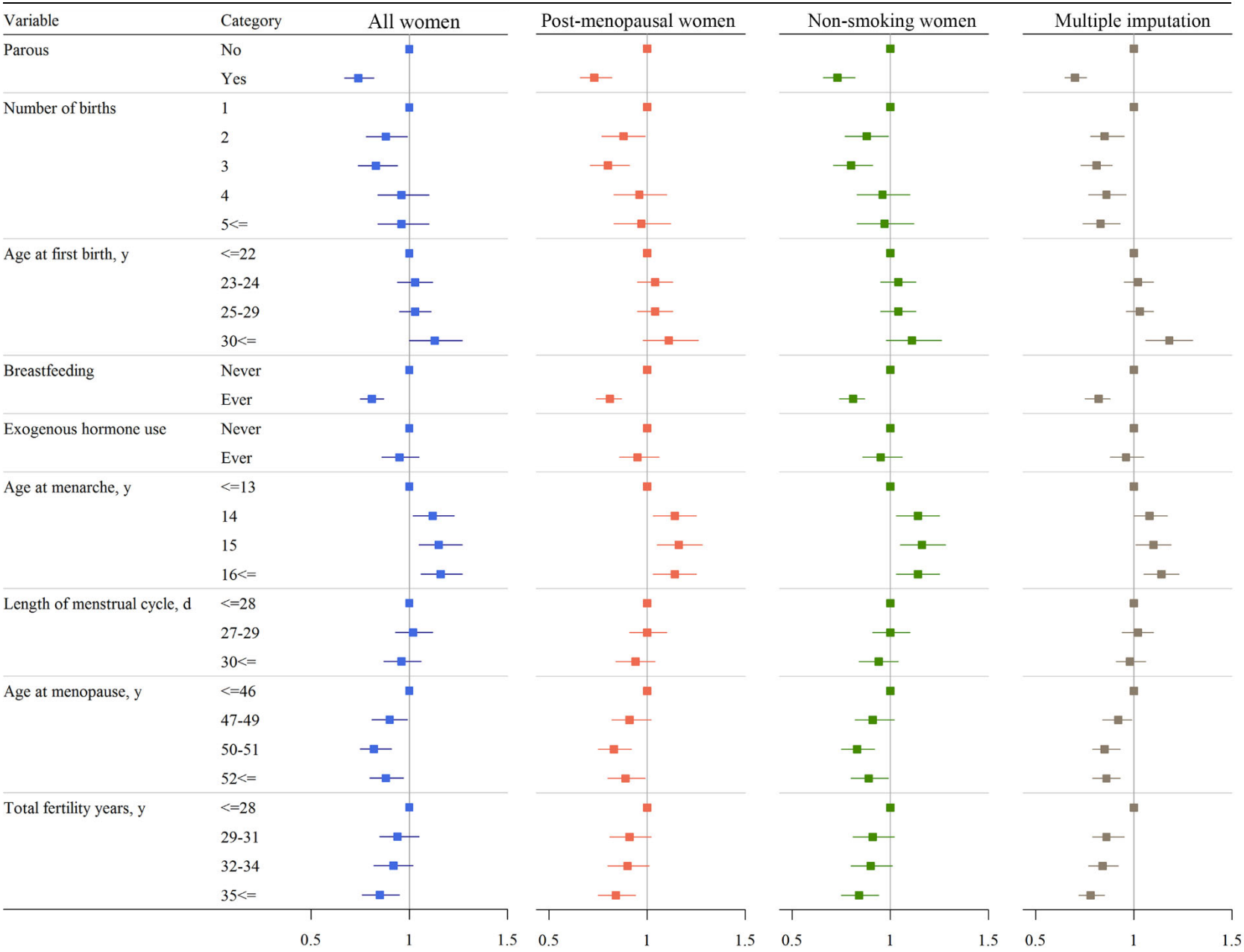


Figure 2-5: Estimations from all women, postmenopausal women, women with non-smoking, and multiply imputed data for all-cause mortality

Table 2-14: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with reproduction-related factors and hormone use in naturally menopausal women in the JPHC Study

Variables	Person-years	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Parous											
No	26,323	328	1.00 (reference)[b]	115	1.00 (reference)[b]	80	1.00 (reference)[b]	39	1.00 (reference)[b]	17	1.00 (reference)[b]
Yes	374,846	3,355	0.79 (0.71–0.89)	1,158	0.75 (0.61–0.91)	431	0.79 (0.57–1.08)	359	0.67 (0.48–0.95)	219	1.01 (0.61–1.67)
Number of births[c]											
1	28,357	280	1.00 (reference)[b]	102	1.00 (reference)[b]	41	1.00 (reference)[b]	39	1.00 (reference)[b]	13	1.00 (reference)[b]
2	121,756	920	0.85 (0.75–0.98)	327	0.80 (0.64–1.01)	115	0.74 (0.51–1.06)	30	0.79 (0.52–1.19)	53	1.21 (0.65–2.23)
3	109,934	891	0.86 (0.75–0.99)	308	0.80 (0.64–1.01)	129	0.86 (0.60–1.24)	92	0.99 (0.66–1.50)	69	1.56 (0.85–2.85)
4	55,685	575	0.99 (0.85–1.15)	196	0.95 (0.74–1.21)	78	0.93 (0.63–1.38)	111	0.96 (0.61–1.51)	38	1.46 (0.76–2.80)
≥5	59,115	689	0.95 (0.81–1.10)	225	0.90 (0.70–1.17)	111	1.05 (0.71–1.56)	58	0.98 (0.62–1.57)	46	1.33 (0.69–2.57)
P_{trend}[d]			0.34		0.69		0.16	68	0.45		0.37
Age at first birth, y[c]											
≤22	88,293	832	1.00 (reference)[b]	280	1.00 (reference)[b]	113	1.00 (reference)[b]	87	1.00 (reference)[b]	57	1.00 (reference)[b]
23–24	98,475	904	1.06 (0.96–1.17)	308	1.04 (0.89–1.23)	133	1.19 (0.92–1.54)	93	1.07 (0.80–1.44)	52	0.93 (0.63–1.36)
25–29	153,622	1,314	1.07 (0.98–1.17)	467	1.09 (0.93–1.27)	183	1.13 (0.89–1.45)	144	1.15 (0.87–1.51)	90	1.13 (0.80–1.60)
≥30	34,455	305	1.11 (0.97–1.26)	103	1.08 (0.86–1.36)	45	1.25 (0.88–1.78)	35	1.24 (0.83–1.85)	20	1.03 (0.62–1.74)
P_{trend}[d]			0.10		0.10		0.25		0.22		0.52
Breastfeeding[c]											
Never	37,960	316	1.00 (reference)[b]	104	1.00 (reference)[b]	36	1.00 (reference)[b]	36	1.00 (reference)[b]	22	1.00 (reference)[b]
Ever	333,547	3,039	0.83 (0.76–0.91)	1,054	0.86 (0.74–0.99)	395	0.92 (0.72–1.18)	323	0.74 (0.57–0.96)	197	0.86 (0.61–1.23)
Exogenous hormone use											
Never use	357,757	3,378	1.00 (reference)[e]	1,160	1.00 (reference)[e]	474	1.00 (reference)[e]	360	1.00 (reference)[e]	216	1.00 (reference)[e]
Ever use	43,411	305	0.95 (0.84–1.07)	113	0.96 (0.79–1.18)	44	1.00 (0.72–1.37)	38	1.02 (0.73–1.45)	20	1.10 (0.68–1.76)

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use among women with naturally menopause

[b] Adjustments as in footnote a except parity due to collinearity

[c] Parous women only

[d] *P* value for linear trend across categories of variable

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

Table 2-15: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with menstruation-related factors in naturally menopausal women in the JPHC Study

Variables	Person-years	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Age at menarche, y											
≤13	68,756	473	1.00 (reference)[b]	162	1.00 (reference)[b]	62	1.00 (reference)[b]	53	1.00 (reference)[b]	21	1.00 (reference)[b]
14	82,566	693	1.12 (1.00–1.26)	259	1.26 (1.03–1.54)	96	1.15 (0.84–1.59)	69	0.97 (0.67–1.39)	48	1.71 (1.02–2.87)
15	92,957	819	1.14 (1.02–1.28)	288	1.21 (1.00–1.48)	126	1.31 (0.97–1.79)	90	1.09 (0.77–1.53)	59	1.81 (1.09–2.99)
≥16	156,890	1,698	1.14 (1.02–1.27)	564	1.21 (1.00–1.45)	234	1.13 (0.85–1.52)	186	1.15 (0.84–1.58)	108	1.41 (0.87–2.29)
P_{trend}[c]			0.05		0.18		0.53		0.23		0.58
Menstrual cycle, d											
≤26	49,928	431	1.00 (reference)	142	1.00 (reference)	65	1.00 (reference)	26	1.00 (reference)	44	1.00 (reference)
27–29	180,559	1,635	0.98 (0.88–1.10)	558	1.03 (0.85–1.24)	246	0.99 (0.75–1.31)	187	1.97 (1.30–2.98)	86	0.48 (0.33–0.69)
≥30	105,624	1,067	0.93 (0.83–1.04)	380	1.05 (0.86–1.28)	135	0.76 (0.56–1.02)	121	1.92 (1.25–2.96)	66	0.51 (0.34–0.75)
P_{trend}[c]			0.12		0.63		0.02		0.03		0.01
Age at menopause, y[d]											
≤46	65,314	649	1.00 (reference)[b]	191	1.00 (reference)[b]	94	1.00 (reference)[b]	75	1.00 (reference)[b]	45	1.00 (reference)[b]
47–49	114,131	944	0.90 (0.81–0.99)	324	1.02 (0.85–1.22)	131	0.86 (0.66–1.13)	101	0.83 (0.61–1.12)	65	0.93 (0.58–1.48)
50–51	117,294	1,032	0.82 (0.75–0.91)	369	1.00 (0.84–1.19)	147	0.79 (0.61–1.03)	105	0.74 (0.54–0.99)	65	0.72 (0.44–1.15)
≥52	104,429	1,058	0.88 (0.80–0.97)	389	1.13 (0.95–1.35)	146	0.80 (0.62–1.04)	117	0.83 (0.62–1.12)	61	0.71 (0.44–1.16)
P_{trend}[c]			0.01		0.17		0.10		0.24		0.04
Total fertility span, y[e]											
≤28	30,489	355	1.00 (reference)[b]	93	1.00 (reference)[b]	57	1.00 (reference)[b]	41	1.00 (reference)[b]	30	1.00 (reference)[b]
29–31	53,171	532	0.92 (0.80–1.05)	176	1.15 (0.90–1.49)	70	0.75 (0.53–1.07)	63	0.92 (0.62–1.37)	34	0.68 (0.41–1.11)
32–34	115,002	1,049	0.89 (0.79–1.01)	358	1.14 (0.90–1.44)	150	0.81 (0.59–1.10)	106	0.75 (0.52–1.08)	70	0.71 (0.46–1.10)
≥35	202,506	1,747	0.83 (0.74–0.93)	646	1.14 (0.91–1.43)	241	0.70 (0.52–0.95)	188	0.73 (0.52–1.04)	102	0.59 (0.39–0.89)
P_{trend}[c]			<0.01		0.43		0.04		0.04		0.03

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity(0,1,2,3,4,5+); total fertility span; and exogenous hormones use among women with naturally menopause

[b] Adjustments as in footnote a except total fertility span due to collinearity

[c] *P* value for linear trend across categories of variable

[d] Naturally menopausal women only

[e] Interval between age at menarche and natural menopause

Table 2-16: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with reproduction-related factors and hormone use in never-smokers in the JPHC Study

Variables	Person-years	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Parous											
No	47,489	376	1.00 (reference)[b]	147	1.00 (reference)[b]	44	1.00 (reference)[b]	38	1.00 (reference)[b]	21	1.00 (reference)[b]
Yes	721,581	3,910	0.73 (0.66–0.82)	1,516	0.71 (0.59–0.85)	486	0.73 (0.53–1.00)	401	0.69 (0.49–0.98)	214	0.74 (0.46–1.17)
Number of births[c]											
1	52,129	311	1.00 (reference)[b]	130	1.00 (reference)[b]	38	1.00 (reference)[b]	30	1.00 (reference)[b]	14	1.00 (reference)[b]
2	277,951	1,226	0.88 (0.77–0.99)	509	0.81 (0.67–0.99)	123	0.75 (0.52–1.08)	115	0.85 (0.56–1.27)	55	1.06 (0.58–1.91)
3	223,926	1,031	0.80 (0.71–0.91)	405	0.74 (0.60–0.90)	131	0.83 (0.57–1.19)	124	1.00 (0.66–1.49)	67	1.26 (0.70–2.26)
4	92,448	630	0.96 (0.83–1.10)	232	0.88 (0.70–1.10)	80	0.95 (0.64–1.41)	60	1.00 (0.63–1.56)	36	1.17 (0.62–2.22)
≥5	75,126	712	0.97 (0.83–1.12)	240	0.87 (0.69–1.11)	114	1.14 (0.76–1.71)	72	1.16 (0.73–1.84)	42	1.07 (0.55–2.05)
P_{trend}[d]			0.49		0.73		0.06		0.18		0.80
Age at first birth, y[c]											
≤22	152,710	920	1.00 (reference)[b]	338	1.00 (reference)[b]	117	1.00 (reference)[b]	101	1.00 (reference)[b]	49	1.00 (reference)[b]
23–24	197,084	1,077	1.04 (0.95–1.13)	412	1.03 (0.89–1.20)	138	1.13 (0.88–1.46)	115	1.03 (0.79–1.36)	50	0.99 (0.66–1.47)
25–29	306,384	1,555	1.04 (0.95–1.13)	629	1.08 (0.94–1.24)	188	1.09 (0.86–1.39)	148	0.92 (0.71–1.20)	94	1.30 (0.91–1.86)
≥30	65,403	358	1.11 (0.98,1.26)	137	1.12 (0.91–1.37)	43	1.13 (0.79–1.61)	37	1.09 (0.74–1.60)	21	1.19 (0.71–2.00)
P_{trend}[d]			0.15		0.18		0.49		0.18		0.16
Breastfeeding[c]											
Never	137,001	799	1.00 (reference)[b]	319	1.00 (reference)[b]	81	1.00 (reference)[b]	78	1.00 (reference)[b]	41	1.00 (reference)[b]
Ever	626,194	3,446	0.81 (0.74–0.87)	1,329	0.82 (0.72–0.93)	443	0.93 (0.73–1.19)	358	0.83 (0.65–1.07)	191	0.81 (0.57–1.14)
Exogenous hormone use											
Never use	676,855	3,892	1.00 (reference)[e]	1,504	1.00 (reference)[e]	478	1.00 (reference)[e]	395	1.00 (reference)[e]	217	1.00 (reference)[e]
Ever use	92,215	394	0.95 (0.86–1.06)	159	0.93 (0.79–1.10)	52	1.10 (0.82–1.48)	44	0.97 (0.70–1.34)	18	0.91 (0.55–1.49)

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use among never smoking women

[b] Adjustments as in footnote a except parity due to collinearity

[c] Parous women only

[d] *P* value for linear trend across categories of variable

[e] Adjustments as in footnote a except exogenous hormones use due to collinearity

Table 2-17: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and major causes of death associated with menstruation-related factors in never-smokers in the JPHC Study

Variables	Person-years	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Age at menarche, y											
≤13	234,587	760	1.00 (reference)[b]	338	1.00 (reference)[b]	73	1.00 (reference)[b]	71	1.00 (reference)[b]	25	1.00 (reference)[b]
14	193,166	929	1.14 (1.03,1.25)	392	1.17 (1.00–1.35)	111	1.24 (0.92–1.67)	93	1.14 (0.83–1.56)	44	1.40 (0.85–2.29)
15	158,341	960	1.16 (1.05–1.28)	373	1.15 (0.99–1.35)	123	1.32 (0.98–1.77)	102	1.22 (0.89–1.67)	61	1.73 (1.08–2.78)
≥16	182,975	1,637	1.14 (1.03–1.25)	560	1.10 (0.94–1.29)	218	1.15 (0.86–1.53)	173	1.25 (0.92–1.70)	105	1.39 (0.87–2.20)
P_{trend}[c]			0.03		0.35		0.57		0.15		0.27
Menstrual cycle, d											
≤26	126,169	568	1.00 (reference)	238	1.00 (reference)	69	1.00 (reference)	34	1.00 (reference)	44	1.00 (reference)
27–29	324,236	1,855	1.00 (0.91–1.10)	703	0.97 (0.83–1.12)	247	1.02 (0.77–1.34)	205	1.84 (1.27–2.66)	85	0.49 (0.34–0.71)
≥30	186,775	1,167	0.94 (0.84–1.04)	455	0.97 (0.83–1.14)	138	0.81 (0.60–1.09)	121	1.67 (1.13–2.47)	62	0.51 (0.34–0.75)
P_{trend}[c]			0.12	138	0.80		0.08		0.08		0.01
Age at menopause, y[d]											
≤46	59,863	570	1.00 (reference)[b]	171	1.00 (reference)[b]	84	1.00 (reference)[b]	62	1.00 (reference)[b]	41	1.00 (reference)[b]
47–49	105,246	847	0.91 (0.82–1.02)	289	1.02 (0.84–1.23)	115	0.85 (0.64–1.13)	90	0.88 (0.64–1.23)	60	0.91 (0.61–1.36)
50–51	110,888	946	0.83 (0.75–0.92)	338	0.99 (0.82–1.20)	130	0.75 (0.57–1.00)	97	0.81 (0.58–1.12)	62	0.71 (0.48–1.06)
≥52	99,530	978	0.89 (0.80–0.99)	365	1.14 (0.94–1.37)	136	0.80 (0.60–1.05)	108	0.90 (0.65–1.24)	54	0.65 (0.43–0.98)
P_{trend}[c]			0.02		0.16		0.10		0.56		0.02
Total fertility span, y[e]											
≤28	156,720	554	1.00 (reference)[b]	225	1.00 (reference)[b]	65	1.00 (reference)[b]	50	1.00 (reference)[b]	30	1.00 (reference)[b]
29–31	154,262	689	0.91 (0.81–1.02)	264	0.96 (0.79–1.15)	74	0.74 (0.53–1.05)	80	1.07 (0.74–1.55)	37	0.76 (0.46–1.23)
32–34	188,168	1,181	0.90 (0.80–1.01)	449	1.04 (0.86–1.27)	153	0.81 (0.59–1.11)	113	0.84 (0.58–1.22)	71	0.76 (0.48–1.19)
≥35	269,919	1,862	0.84 (0.75–0.94)	725	1.04 (0.86–1.26)	238	0.69 (0.51–0.93)	196	0.86 (0.60–1.23)	97	0.56 (0.36–0.87)
P_{trend}[c]			<0.01		0.48		0.03		0.22		0.01

[a] Cox proportional hazards models stratified by age and public health center area and adjusted for BMI; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity(0,1,2,3,4,5+); total fertility span; and exogenous hormones use among never smoking women

[b] Adjustments as in footnote a except total fertility span due to collinearity

[c] *P* value for linear trend across categories of variable

[d] Naturally menopausal women only

[e] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

Table 2-18: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality associated with reproduction-related factors and hormone use using multiple imputed datasets in the JPHC Study

Variables	Person-years [a]	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]
Parous											
No	75,969	677	1.00 (reference)[c]	255	1.00 (reference)[c]	95	1.00 (reference)[c]	73	1.00 (reference)[c]	39	1.00 (reference)[c]
Yes	1,025,994	6,490	0.70 (0.65–0.76)	2,345	0.69 (0.59–0.79)	884	0.64 (0.51–0.80)	698	0.69 (0.53–0.89)	480	0.73 (0.51–1.04)
Number of births[d]											
1	81,478	569	1.00 (reference)[c]	213	1.00 (reference)[c]	78	1.00 (reference)[c]	62	1.00 (reference)[c]	24	1.00 (reference)[c]
2	385,176	1,931	0.85 (0.78–0.95)	757	0.83 (0.71–0.98)	230	0.75 (0.57–0.99)	200	0.83 (0.61–1.12)	88	1.13 (0.68–1.86)
3	308,751	1,719	0.81 (0.73–0.89)	651	0.81 (0.69–0.96)	230	0.73 (0.55–0.95)	192	0.83 (0.61–1.12)	120	1.43 (0.88–2.34)
4	133,391	1,035	0.86 (0.77–0.96)	343	0.83 (0.69–0.99)	141	0.73 (0.54–0.99)	112	0.86 (0.62–1.21)	64	1.16 (0.70–1.93)
≥5	117,197	1,234	0.83 (0.74–0.93)	381	0.80 (0.66–0.98)	205	0.82 (0.61–1.10)	132	0.91 (0.65–1.27)	83	1.10 (0.65–1.85)
P_{trend}[e]			0.02		0.11		0.57		0.97		0.99
Age at first birth, y[d]											
≤22	230,953	1,607	1.00 (reference)[c]	551	1.00 (reference)[c]	213	1.00 (reference)[c]	178	1.00 (reference)[c]	98	1.00 (reference)[c]
23–24	275,936	1,737	1.02 (0.95–1.10)	632	1.04 (0.92–1.17)	246	1.17 (0.95–1.43)	191	1.03 (0.83–1.28)	91	0.97 (0.71–1.32)
25–29	423,588	2,516	1.03 (0.96–1.10)	930	1.05 (0.94–1.17)	337	1.10 (0.91–1.34)	256	0.96 (0.78–1.18)	154	1.13 (0.85–1.50)
≥30	95,516	629	1.18 (1.06–1.30)	232	1.16 (0.98–1.37)	82	1.30 (0.99–1.71)	73	1.22 (0.91–1.65)	36	1.14 (0.72–1.72)
P_{trend}[e]			0.02		0.14		0.13		0.62		0.32
Breastfeeding[d]											
Never	132,072	772	1.00 (reference)[c]	277	1.00 (reference)[c]	88	1.00 (reference)[c]	82	1.00 (reference)[c]	45	1.00 (reference)[c]
Ever	893,922	5,718	0.82 (0.75–0.88)	2,067	0.89 (0.78–1.02)	793	0.87 (0.69–1.10)	616	0.82 (0.64–1.06)	333	0.64 (0.46–0.90)
Exogenous hormone use											
Never use	963,143	6,483	1.00 (reference)[f]	2,333	1.00 (reference)[f]	889	1.00 (reference)[f]	685	1.00 (reference)[f]	383	1.00 (reference)[f]
Ever use	138,819	684	0.96 (0.88–1.05)	267	0.94 (0.82–1.08)	87	0.99 (0.79–1.26)	85	1.08 (0.85–1.38)	35	0.96 (0.65–1.42)

[a] Calculations for person-years and the number of cases across categories were based on pooled estimates from all imputed dataset.

[b] Cox proportional hazards models stratified by age (category) and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use using multiply imputed datasets. Multiple imputation by the chained equations approach with 20 iterations was performed to impute missing values by including all covariates, person-years, mortality status, regularity of menstrual cycle, past history of gynecological diseases, age at first pregnancy and number of pregnancies. Estimations were then combined using Rubin's rules (the STATA mi procedure). Estimations were restricted to parous women for breastfeeding and age at first birth.

[c] Adjustments as in footnote a except parity due to collinearity

[d] Parous women only

[e] *P* value for linear trend across categories of variable

[f] Adjustments as in footnote a except exogenous hormones use due to collinearity

Table 2-19: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality associated with menstruation-related factors using multiple imputed datasets in the JPHC Study

Variables	Person-years [a]	All-cause mortality		Cancer		Heart disease		Cerebrovascular disease		Respiratory disease	
		Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]	Cases [a]	HR (95% CI) [b]
Age at menarche, y											
≤13	319,041	1,162	1.00 (reference)[c]	488	1.00 (reference)[c]	120	1.00 (reference)[c]	114	1.00 (reference)[c]	48	1.00 (reference)[c]
14	265,856	1,432	1.08 (1.00–1.17)	555	1.10 (0.97–1.25)	189	1.22 (0.96–1.55)	142	1.04 (0.81–1.36)	78	1.14 (0.78–1.66)
15	225,594	1,522	1.10 (1.01–1.19)	565	1.12 (0.98–1.28)	208	1.20 (0.77–1.62)	178	1.23 (0.96–1.58)	85	1.12 (0.77–1.62)
≥16	291,470	3,050	1.14 (1.05–1.23)	993	1.14 (1.04–1.30)	460	1.21 (0.81–1.61)	337	1.21 (0.95–1.54)	207	1.14 (0.81–1.61)
P_{trend}[d]			<0.01		0.06		0.20		0.08		0.54
Menstrual cycle, d											
≤26	212,740	1,124	1.00 (reference)	420	1.00 (reference)	144	1.00 (reference)	103	1.00 (reference)	76	1.00 (reference)
27–29	554,040	3,552	1.02 (0.94–1.10)	1,308	1.04 (0.92–1.17)	492	1.03 (0.84–1.26)	388	1.23 (0.96–1.59)	193	0.73 (0.54–0.99)
≥30	335,182	2,490	0.98 (0.91–1.06)	873	1.03 (0.90–1.17)	119	0.89 (0.72–1.11)	280	1.22 (0.94–1.58)	149	0.72 (0.52–0.98)
P_{trend}[d]			0.42		0.74		0.16		0.22		0.07
Age at menopause, y[e]											
≤46	98,174	1,083	1.00 (reference)[c]	316	1.00 (reference)[c]	172	1.00 (reference)[c]	124	1.00 (reference)[c]	84	1.00 (reference)[c]
47–49	159,863	1,444	0.92 (0.84–0.99)	480	1.01 (0.86–1.17)	215	0.87 (0.70–1.08)	152	0.85 (0.66–1.10)	97	0.84 (0.62–1.14
50–51	168,489	1,686	0.85 (0.79–0.93)	554	0.97 (0.84–1.12)	259	0.82 (0.67–1.01)	186	0.85 (0.67–1.08)	115	0.75 (0.56–1.01)
≥52	146,106	1,543	0.86 (0.79–0.93)	545	1.06 (0.91–1.23)	230	0.77 (0.63–0.95)	171	0.82 (0.64–1.04)	93	0.69 (0.50–0.94)
P_{trend}[d]			<0.01		0.51		0.02		0.15		0.01
Total fertility span, y[f]											
≤28	230,701	1,009	1.00 (reference)[c]	359	1.00 (reference)[c]	135	1.00 (reference)[c]	107	1.00 (reference)[c]	65	1.00 (reference)[c]
29–31	223,418	1,246	0.86 (0.79–0.95)	465	0.97 (0.83–1.14)	156	0.76 (0.58–0.96)	149	0.92 (0.70–1.22)	65	0.71 (0.49–1.02)
32–34	267,972	1,946	0.84 (0.77–0.92)	692	0.96 (0.82–1.13)	279	0.81 (0.63–0.99)	190	0.72 (0.55–0.95)	123	0.74 (0.54–1.03)
≥35	379,871	2,964	0.78 (0.72–0.85)	1,084	0.95 (0.81–1.10)	409	0.68 (0.54–0.83)	325	0.74 (0.57–0.96)	165	0.57 (0.41–0.78)
P_{trend}[d]			<0.01		0.48		<0.01		<0.01		<0.01

[a] Calculations for person-years and the number of cases across categories were based on pooled estimates from all imputed datasets.

[b] Cox proportional hazards models stratified by age (category) and public health center area and adjusted for BMI; smoking status; alcohol consumption; history of hypertension; history of diabetes; leisure-time sports or physical exercise; total energy intake; intakes of green tea and coffee; job status; living arrangement; parity (0, 1, 2, 3, 4, ≥5); total fertility span; and exogenous hormones use using multiply imputed datasets. Multiple imputation by the chained equations approach with 20 iterations was performed to impute missing values by including all covariates, person-years, mortality status, regularity of menstrual cycle, past history of gynecological diseases, age at first pregnancy and number of pregnancies. Estimations were then combined using Rubin's rules (the STATA mi procedure). Estimations were restricted to post-menopausal women for age at menopause.

[c] Adjustments as in footnote a except total fertility span due to collinearity

[d] *P* value for linear trend across categories of variable

[e] Naturally menopausal women only [f] Interval between age at menarche and natural menopause (for pre-menopausal women, age at recruitment)

2.3. Summary of findings

Based on a large-scale population-based cohort study, results of this study support the vital role played by reproductive factors in the risk of all-cause and major causes of deaths in Japanese women. Protective factors for mortality included parous, two or three births, breastfeeding, late age at menopause and long fertility span. Positive associations were observed among women with late age at menarche and first birth at more than 30 years compared to those aged less than 22. The results from the length of menstrual cycle provided different directions in cause-specific mortality.

3. Female reproductive factors and risk of external cause of death among women: JPHC Study

This chapter describes the methods and materials of the study in section 3.1 and details of methods in subsections 3.1.1 to 3.1.6. The results according to the outcome are shown in section 3.2. Lastly, summary of findings are described in section 3.3.

3.1. Methods and materials

3.1.1. Study design

The data of the JPHC Study was used. Details of the JPHC Study were described in section 2.1.1.

3.1.2. Follow-up and identification of mortality

Detailed information on follow-up and identification of cause-specific mortality was described in section 2.1.2. The major external causes of death in Japanese women were used, namely all external causes (V01–Y89); intentional self-harm, namely suicide (X60–X84, Y87.0); and accidents (V01–X59, Y85–Y86). Participants were followed from the baseline survey (1990, 1993) until death, last confirmation of survival for participants who relocated from the study area (i.e., migration), or end of follow-up (December 31, 2014), whichever occurred first.

3.1.3. Study population

Of the 71,698 women, those with non-Japanese nationality (n=20), pre-commencement emigration (n=86), incorrect birth date (n=5), duplicate registration (n=4) or a late report of migration before the start of the follow-up period (n=4,626) were excluded. Of those remaining, 59,983 women (89.6%) returned the completed questionnaire.

3.1.4. Exclusion criteria

Of eligible subjects, 49,279 (82.1%) completed relevant questions including parity, age at first birth, experience of breastfeeding, age at menarche, age at menopause, exogenous hormone use, height, weight, smoking habits, alcohol consumption, perceived stress level, living with a spouse, and history of disease including cancer, stroke, heart disease, diabetes mellitus, and hypertension. The study schema is visually presented in Figures 3-1.

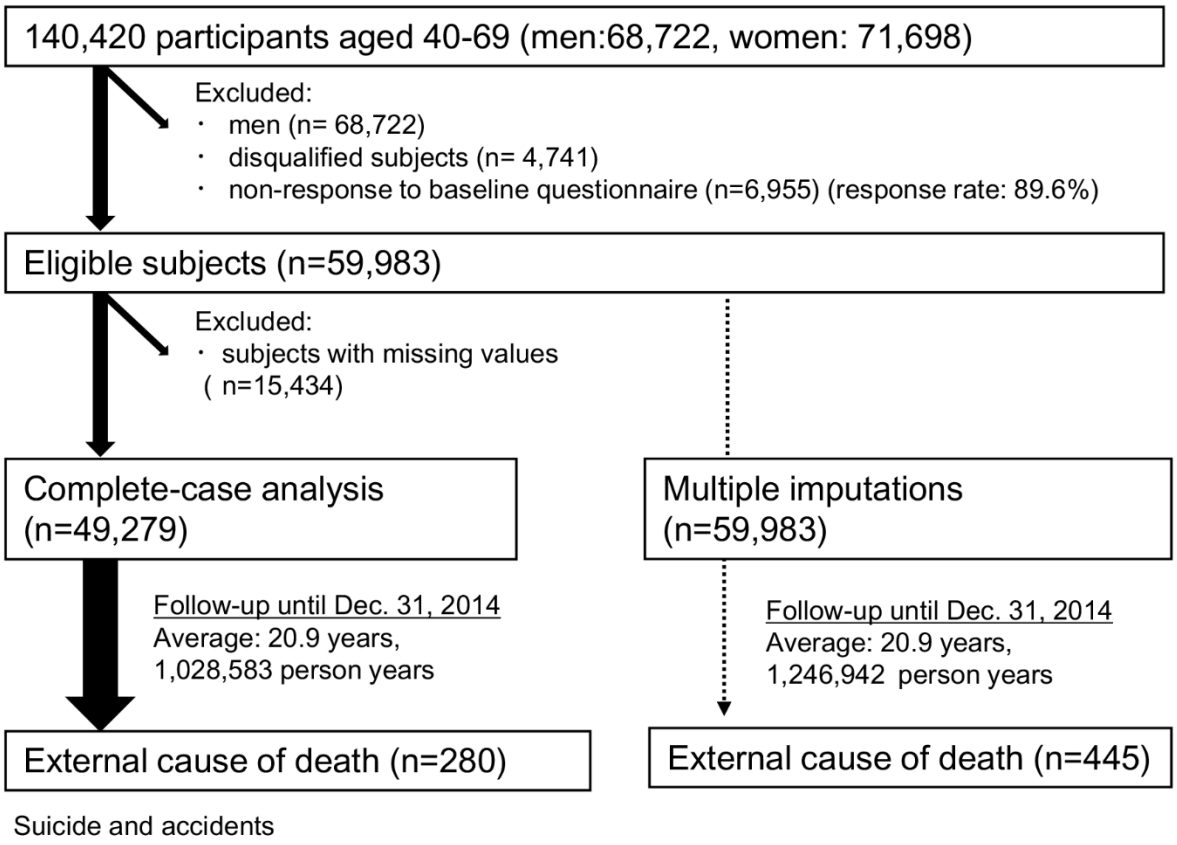


Figure 3-1: Study flow of the JPHC Study for external causes of death

3.1.5. Reproductive factors as exposure variables

Reproductive events captured at the baseline survey were selected as described in section 2.1.5. Selected factors were categorized into binary or tertile groups based on the frequency distribution of variables within the cohort because of the small number of events (Table 3-1). Some unreliable values were identified and replaced with missing value as described in section 2.1.5. The validity of exposure variables was described in section 2.1.6.

Table 3-1: Categorization of female reproductive factors

Variable	Category
Parity	Nulliparous, or parous
Number of birth (births)	(Nulliparous,) 1, 2, 3, or ≥4
Age at first birth (years)	(Nulliparous,) ≤23, 24-26, or ≥27
Breastfeeding	(Nulliparous,) no, or yes
Age at menarche (years)	≤13, 14-15, or ≥16
Exogenous hormone use	Never, or ever
Menopausal status	Pre, post, or surgical menopause
Age at menopause (years)	(Pre-menopause,) ≤47, 48-50, or ≥51
Total fertility years (years)	(Pre-menopause,) ≤32, 33-36, or ≥37

3.1.6. Other covariates

Potential confounders associated with mortality were selected based on prior research as listed in Table 3-2. The detail information on covariates were described in section 2.1.7. Additional variables were perceived stress level (a little, average, or stressful) and past history of disease including cancer, stroke, heart disease, diabetes mellitus, and hypertension (no, or yes). Living with a spouse was used as a surrogate of marital status. Breastfeeding and age at first birth were included in the second model when analyses were restricted to parous women.

Table 3-2: Categorization of covariates according to outcomes

Variable	Category
Age (years)	≤44, 45-49, 50-54, 55-59, or ≥60
PHC	11 areas
BMI (kg/m2)	<21.9, 22-24.9, or ≥25
Smoking (per day)	Never, or ever
Alcohol consumption (per week)	no, occasional, or regular
Living arrangement	Living with a spouse or not
History of disease	No, or yes
Perceived stress level	A little, average, or stressful

3.1.5. Statistical analysis

Cox proportional hazards regression models were conducted to estimate hazard ratios (HR) and 95% confidence intervals (CI) to assess the risk of death by external cause of deaths according to reproductive factors. Participants who were missing information on relevant reproductive factors or other covariates were excluded, leaving a total of 49,279 women in the primary analyses. Proportional hazard assumptions of all variables were verified using Schoenfeld residuals. Because age was found to violate the proportional hazards assumption, attained age was used as the time scale for all models [125].

The minimum model (Model B1) was built with stratification by 11 study areas to allow a different baseline hazard due to the varying distribution of suicide rates across Japan [97]. The second model (Model B2) was adjusted for a priori covariates and several reproductive factors as follows: body mass index (BMI, in kg/m^2; <21.9, 22 to 24.9, or ≥25); smoking status (never or ever); alcohol consumption (no, occasional, or regular); perceived stress level (a little, average, stressful); living with spouse; past history of disease, including cancer, stroke, heart disease, diabetes mellitus, and hypertension (no, or yes); parity; age at menarche; menopausal status; and exogenous hormone use.

Effects of *p*-values for linear trends were assessed for parity, age at first birth, age at menarche, length of menstrual cycle, age at menopause and total fertility years by assigning ordinal variables. A likelihood ratio test was conducted to compare models with and without interaction terms and to calculate a *p*-value for statistical interaction between reproductive factors and confounders. Stratified

analysis by menopausal status at baseline was conducted because menopausal transition or menopausal status is likely to be a high risk for suicide or accidents.

All *p*-values reported were two-sided, and $p < 0.05$ was set as the significance level. All analyses were performed with STATA version 14.0 software (StataCorp LP).

3.1.6. Multiple imputations as sensitivity analysis

For sensitivity analysis, multiple imputation procedures were employed to impute missing values in order to assess the degree of selection bias due to complete case analysis. Cox proportional hazards models using multiple imputed datasets was conducted using attained age as time scale stratified by 11 public health center areas and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse, history of disease, parity, age at menarche, menopausal status and exogenous hormone use. Multiple imputations by the chained equations approach with 20 iterations were performed to impute missing values by including all covariates, person-years, and vital status. Estimations were then combined using Rubin's rules (the STATA mi procedure). Estimations were restricted to parous women for breastfeeding and age at first birth, and to postmenopausal women for age at menopause and total fertility years. Calculations for person-years and the number of cases across categories were a mean of estimations from all imputed datasets.

3.2. Results

3.2.1. Basic characteristics

During 1,028,583 person-years (an average of 20.9 years) of follow-up for 49,279 women, a total of 328 deaths by all external causes, 148 suicides (45%), and 167 accidents (51%) were identified. The median age of death was 63 years old (IQR=56–71) for suicide and 69 years old (IQR=61–75) for accidents. In comparison with the age of deaths from all causes (73 years old, IQR=65–80), study subjects died 10 earlier years by suicide.

When comparing subjects with and without missing data for all relevant variables, 17.9% of subjects had at least one missing datum (Table 3-3). Among subjects, 53.7% of women reported their pre-menopausal status at baseline survey. Several variables varied by menopausal status; pre-menopausal women were younger, reported less breastfeeding, younger age at menarche and more exogenous hormones use compared with post-menopausal women. Suicide and accidents occurred more in postmenopausal women compared to premenopausal women, while the gap in the percentage of mortality between pre- and post-menopause was smaller in suicide than accidents.

Table 3-3: Basic characteristics of study subjects at baseline survey for analysis of external causes of death in the JPHC Study

Characteristic	Eligible subjects	*Among eligible subjects*			*Among subjects with complete data*		
		Subjects with a missing value	Subjects with complete data	*P*[a]	Pre-menopause	Post-menopause	*P*[a]
Number of subjects (n)	59,983	10,704 (17.9%)	49,279 (82.1%)		26,456 (53.7%)	22,824 (46.3%)	
Age at recruitment, y, mean (SD)	51.6 (8.0)	54.7 (8.1)	50.9 (7.8)	<0.01	44.6 (4.0)	56.3 (6.1)	<0.01
BMI (kg/m^2), mean (SD)	23.4 (3.3)	23.6 (4.1)	23.3 (3.2)	0.01	23.1 (3.1)	23.6 (3.3)	<0.01
Never smoker, %	90.5	91.1	90.3	<0.01	88.2	83.1	<0.01
Non-drinker, %	75.4	81.2	74.2	<0.01	66.5	80.8	<0.01
High perceived stress, %	19.1	19.1	16.5	<0.01	23.2	16.5	<0.01
Living with spouse, %	78.3	74.1	79.2	<0.01	82.7	76.2	<0.01
History of diseases, %	19.9	23.1	19.2	<0.01	3.9	27.7	<0.01
Reproductive factors							
Parity, mean (SD)[b]	2.7 (1.5)	2.9 (1.8)	2.6 (1.5)	<0.01	2.4 (1.2)	2.8 (1.7)	<0.01
Age at first birth, y, mean (SD)[b]	25.0 (3.5)	24.7 (3.6)	25.0 (3.5)	<0.01	25.2 (3.5)	24.9 (3.5)	<0.01
Ever breastfed, %[b]	86.8	86.6	86.8	0.67	84.5	88.9	<0.01
Age at menarche, y, mean (SD)	14.6 (1.9)	15.4 (2.2)	14.5 (1.8)	<0.01	13.7 (1.5)	15.1 (1.9)	<0.01
Age at menopause, y, mean (SD)[c]	48.1	47.9 (5.5)	48.1 (4.8)	0.01		48.1 (4.8)	
Total fertility years, y, mean (SD)[c]	32.8	32.1 (5.4)	33.0 (4.8)	<0.01		33.0 (4.8)	
Ever use of exogenous hormone, %	13.2	12.2	13.4	<0.01	14.0	12.8	<0.01
Outcome							
All external causes, %	445	125 (28.1)	320 (71.9)		100 (31.3)	220 (68.8)	
Suicide, %	194	40 (20.6)	154 (79.4)		64 (41.6)	80 (58.4)	
Accidents, %	205	52 (25.4)	153 (74.6)		32 (20.9)	121 (79.1)	

BMI, body mass index; n, number; SD, standard deviation; y, year

[a] Analysis of variance (ANOVA) for continuous variables or chi-square test for categorical variables

[b] Parous women only

[c] Post-menopause only

3.2.2. All injuries

Tables 3-4 and 3-5 present unadjusted and multivariable-adjusted HRs with 95% CIs of mortality risk by all external causes according to female reproductive factors for all women, with estimations for stratified analyses by menopausal status. A decreased risk of all external causes was observed in parous women with ever breastfeeding [0.67 (95%CI: 0.49–0.92)]. A marginally inverse association was found in women with three births compared to the reference group [2 births: reference; 1 birth: 1.07 (95%CI: 0.71–1.62); 3 births: 0.75 (95%CI: 0.55–1.01); ≥4births: 0.99 (95%CI: 0.62–1.57); P_{trend}: 0.74]. A suggestive increased risk trend was found in women with later age at menarche (≤13 years: reference; 14–15: 1.48 (95%CI: 1.09–2.00); ≥16: 1.38 (95%CI: 0.97–1.96); P_{trend}: 0.07]. In stratified analysis, increased risk due to late age at menarche was more pronounced among pre-menopausal women. However, there was no statistically significant interaction among all reproductive factors.

Table 3-4: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by all external causes according to reproductive factors for all women, pre-menopausal women, and post-menopausal women in the JPHC Study

Variable	Category	Person–years	All women			Pre–menopause		Post–menopause		P_{int}
			Cases	Model B1[a]	Model B2[b]	Cases	Model B2[b]	Cases	Model B2[b]	
				HR (95%CI)	HR (95%CI)		HR (95%CI)		HR (95%CI)	
Parous	No	71,289	31	1.00 (reference)	1.00 (reference)[c]	13	1.00 (reference)[c]	18	1.00 (reference)[c]	0.18
	Yes	957,293	298	0.67 (0.46–0.97)	0.77 (0.52–1.15)	88	0.61 (0.32–1.16)	209	0.90 (0.54–1.48)	
Parity[d]	1	77,207	30	1.24 (0.83–1.86)	1.07 (0.71–1.62)	11	1.09 (0.55–2.15)	19	1.04 (0.62–1.74)	0.45
	2	371,068	117	1.00 (reference)	1.00 (reference)[e]	45	1.00 (reference)[e]	72	1.00 (reference)[e]	
	3	291,703	71	0.74 (0.55–0.99)	0.75 (0.55–1.01)	17	0.53 (0.55–2.15)	54	0.86 (0.60–1.24)	
	≥4	217,314	79	1.06 (0.76–1.48)	0.99 (0.62–1.57)	15	0.94 (0.49–1.80)	64	1.12 (0.75–1.65)	
	P_{trend}[f]			0.34	0.74		0.86		0.58	
Age at first birth, y[d]	≤22	213,668	76	1.00 (reference)	1.00 (reference)[e]	21	1.00 (reference)[e]	55	1.00 (reference)[e]	0.89
	23–26	485,409	142	0.91 (0.68–1.22)	0.95 (0.71–1.27)	43	0.93 (0.54–1.60)	99	0.97 (0.69–1.37)	
	≥27	258,786	79	1.03 (0.74–1.43)	1.01 (0.72–1.43)	24	1.07 (0.57–1.99)	55	1.02 (0.68–1.55)	
	P_{trend}[f]			0.84	0.94		0.82		0.91	
Breastfeeding[d]	Never	125,722	51	1.00 (reference)	1.00 (reference)[e]	22	1.00 (reference)[e]	29	1.00 (reference)[e]	0.59
	Ever	831,570	246	0.64 (0.47–0.88)	0.67 (0.49–0.92)	66	0.62 (0.38–1.02)	180	0.71 (0.47–1.08)	
Exogenous hormone use	Never use	887,175	282	1.00 (reference)	1.00 (reference)	91	1.00 (reference)	191	1.00 (reference)	0.07
	Ever use	141,407	46	1.08 (0.79–1.50)	1.07 (0.78–1.48)	10	0.66 (0.34–1.27)	36	1.31 (0.90–1.90)	
Age at menarche, y	≤13	316,896	65	1.00 (reference)	1.00 (reference)	27	1.00 (reference)	38	1.00 (reference)	0.12
	14–15	466,496	165	1.49 (1.10–2.01)	1.48 (1.09–2.00)	59	1.99 (1.24–3.17)	106	1.15 (0.78–1.69)	
	≥16	245,189	98	1.43 (1.01–2.02)	1.38 (0.97–1.96)	15	2.35 (1.21–4.55)	83	1.03 (0.68–1.56)	
	P_{trend}[f]			0.06	0.07		0.01		0.88	
Menopausal status	Pre-menopause	481,912	101	0.94 (0.62–1.44)	1.00 (reference)					
	Natural menopause	452,624	193	1.00 (reference)	1.00 (reference)					
	Surgical menopause	94,046	34	1.05 (0.60–1.86)	0.89 (0.61–1.30)					

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas
[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use
[c] Adjustments as in footnote b except for parity
[d] Parous women only
[e] Additional adjustment for age at first birth and breastfeeding
[f] *P* value for linear trend across categories of variable

Table 3-5: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by all external causes according to age at menopause and total fertility years in the JPHC Study

Variable	Category	Person–years	Post–menopause		
			Cases	Model B1[a]	Model B2[b]
				HR (95%CI)	HR (95%CI)
Age at menopause, y	≤47	177,875	72	1.00 (reference)	1.00 (reference)
	48–50	210,330	86	0.95 (0.69–1.31)	0.92 (0.65–1.30)
	≥51	158,485	69	0.94 (0.66–1.32)	0.92 (0.63–1.33)
	P_{trend}[c]			0.71	0.66
Total fertility span, y	≤32	204,419	82	1.00 (reference)	1.00 (reference)[d]
	33–35	167,339	70	0.97 (0.70–1.34)	0.94 (0.67–1.33)
	≥36	174,911	75	0.95 (0.69–1.31)	0.92 (0.64–1.33)
	P_{trend}[c]			0.76	0.67

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas
[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use
[c] *P* value for linear trend across categories of variable
[d] Adjustments as in footnote b except for age at menarche

3.2.3. Suicide

A lowered risk of suicide was evident in ever versus never parity [0.53 (95%CI: 0.32–0.88)] (Tables 3-6 and 3-7). Parity with three births was inversely associated with risk of suicide compared to the reference group [2 births: reference; 1 birth: 1.12 (95%CI: 0.61–2.04); 3 births: 0.61 (95%CI: 0.39–0.97); ≥4 births: 0.91 (95%CI: 0.54–1.53); P_{trend}: 0.24].

Table 3-6: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by suicide according to reproductive factors for all women, pre-menopausal women, and post-menopausal women in the JPHC Study

Variable	Category	Person-years	All women			Pre-menopause		Post-menopause		P_{int}
			Cases	Model B1[a]	Model B2[b]	Cases	Model B2[b]	Cases	Model B2[b]	
				HR (95%CI)	HR (95%CI)		HR (95%CI)		HR (95%CI)	
Parous	No	71,289	20	1.00 (reference)	1.00 (reference)[c]	11	1.00 (reference)[c]	9	1.00 (reference)[c]	0.21
	Yes	957,293	128	0.45 (0.28–0.73)	0.53 (0.32–0.88)	54	0.47 (0.23–0.94)	72	0.64 (0.30–1.36)	
Parity[d]	1	77,207	14	1.23 (0.68–2.20)	1.12 (0.61–2.04)	6	0.96 (0.40–2.34)	8	1.21 (0.55–2.65)	0.33
	2	371,068	59	1.00 (reference)	1.00 (reference)[e]	30	1.00 (reference)[e]	29	1.00 (reference)[e]	
	3	291,703	28	0.61 (0.38–0.95)	0.61 (0.39–0.97)	8	0.38 (0.17–0.83)	20	0.83 (0.47–1.49)	
	≥4	217,314	27	0.95 (0.58–1.59)	0.91 (0.54–1.53)	10	0.96 (0.44–2.11)	17	0.95 (0.49–1.85)	
	P_{trend}[f]			0.19	0.24		0.31		0.56	
Age at first birth, y [d]	≤22	213,668	32	1.00 (reference)	1.00 (reference)[e]	14	1.00 (reference)[e]	18	1.00 (reference)[e]	0.72
	23–26	485,409	66	0.91 (0.59–1.41)	0.92 (0.60–1.43)	27	0.79 (0.40–1.56)	39	1.05 (0.59–1.89)	
	≥27	258,786	30	0.87 (0.52–1.46)	0.81 (0.47–1.38)	13	0.82 (0.36–1.84)	17	0.85 (0.42–1.74)	
	P_{trend}[f]			0.61	0.44		0.63		0.66	
Breastfeeding [d]	Never	125,722	23	1.00 (reference)	1.00 (reference)[e]	14	1.00 (reference)[e]	9	1.00 (reference)[e]	0.32
	Ever	831,570	105	0.68 (0.43–1.07)	0.72 (0.45–1.14)	40	0.58 (0.31–1.08)	65	0.94 (0.46–1.93)	
Exogenous hormone use	Never use	887,175	129	1.00 (reference)	1.00 (reference)	59	1.00 (reference)	70	1.00 (reference)	0.28
	Ever use	141,407	19	0.88 (0.54–1.44)	0.85 (0.52–1.40)	6	0.64 (0.27–1.51)	13	1.02 (0.55–1.89)	
Age at menarche, y	≤13	316,896	37	1.00 (reference)	1.00 (reference)	21	1.00 (reference)	16	1.00 (reference)	0.46
	14–15	466,496	75	1.36 (0.91–2.05)	1.36 (0.90–2.05)	35	1.54 (0.89–2.68)	40	1.09 (0.60–2.00)	
	≥16	245,189	36	1.42 (0.86–2.34)	1.37 (0.82–2.28)	9	2.08 (0.92–4.70)	27	0.98 (0.51–1.89)	
	P_{trend}[f]			0.16	0.23		0.08		0.94	
Menopausal status	Pre-menopause	481,912	65	0.94 (0.62–1.44)	1.08 (0.70–1.68)					
	Natural menopause	452,624	68	1.00 (reference)	1.00 (reference)					
	Surgical menopause	94,046	15	1.05 (0.60–1.86)	0.99 (0.56–1.77)					

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas

[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use

[c] Adjustments as in footnote b except for parity

[d] Parous women only

[e] Additional adjustment for age at first birth and breastfeeding

[f] *P* value for linear trend across categories of variable

Table 3-7: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by suicide according to age at menopause and total fertility years in the JPHC Study

Variable	Category	Person-years	Post-menopause		
			Cases	Model B1[a]	Model B2[b]
				HR (95%CI)	HR (95%CI)
Age at menopause, y	≤47	177,875	27	1.00 (reference)	1.00 (reference)
	48–50	210,330	38	1.26 (0.76–2.10)	1.34 (0.76–2.36)
	≥51	158,485	18	0.79 (0.43–1.47)	0.86 (0.44–1.69)
	P_{trend}[c]			0.52	0.64
Total fertility span, y	≤32	204,419	29	1.00 (reference)	1.00 (reference)[d]
	33–35	167,339	32	1.37 (0.82–2.30)	1.43 (0.82–2.51)
	≥36	174,911	22	0.89 (0.50–1.57)	0.93 (0.49–1.78)
	P_{trend}[c]			0.73	0.82

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas
[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use
[c] *P* value for linear trend across categories of variable
[d] Adjustments as in footnote b except for age at menarche

3.2.4. Accidents

Parous women who ever breastfed versus never had a much lower risk of death by accidents [0.63, (95%CI: 0.40–0.97)] (Tables 3-8 and 3-9). Insignificant positive associations were observed among women with late age at menarche [≤13 years: reference; 14–15: 1.55 (95%CI: 0.96–2.51); 16≤:1.54 (95%CI: 0.92–2.60); P_{trend}: 0.10] and ever use of exogenous hormones [1.45 (95%CI: 0.93–2.25)]. The effect of age at menarche was more evident in pre-menopausal women, as was that with post-menopause for exogenous hormone use, although both *p*-values for interaction were not significant.

Table 3-8: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by accident according to reproductive factors for all women, pre-menopausal women, and post-menopausal women in the JPHC Study

Variable	Category	Person-years	All women			Pre-menopause		Post-menopause		P_{int}
			Cases	Model B1[a]	Model B2[b]	Cases	Model B2[b]	Cases	Model B2[b]	
				HR (95%CI)	HR (95%CI)		HR (95%CI)		HR (95%CI)	
Parous	No	71,289	10	1.00 (reference)	1.00 (reference)[c]	1	1.00 (reference)[c]	9	1.00 (reference)[c]	0.54
	Yes	957,293	157	1.12 (0.57–2.21)	1.23 (0.62–2.44)	31	2.02 (0.27–15.3)	113	1.11 (0.54–2.30)	
Parity[d]	1	77,207	14	1.17 (0.65–2.10)	1.10 (0.61–1.99)	5	1.45 (0.52–4.03)	9	0.95 (0.46–1.96)	0.27
	2	371,068	56	1.00 (reference)	1.00 (reference)[e]	16	1.00 (reference)[e]	40	1.00 (reference)[e]	
	3	291,703	40	0.84 (0.56–1.27)	0.83 (0.55–1.26)	9	0.76 (0.33–1.75)	31	0.86 (0.54–1.39)	
	≥4	217,314	47	1.15 (0.73–1.80)	1.13 (0.72–1.77)	4	0.69 (0.21–2.24)	43	0.74 (0.75–2.01)	
	P_{trend}[f]			0.99	0.96		0.23		0.50	
Age at first birth, y[d]	≤22	213,668	40	1.00 (reference)	1.00 (reference)[e]	6	1.00 (reference)[e]	34	1.00 (reference)[e]	0.54
	23–26	485,409	73	0.87 (0.58–1.31)	0.93 (0.62–1.40)	17	1.18 (0.45–3.12)	56	0.87 (0.56–1.37)	
	≥27	258,786	44	1.03 (0.65–1.63)	1.05 (0.65–1.71)	11	1.64 (0.56–4.77)	33	0.93 (0.54–1.61)	
	P_{trend}[f]		44	0.91	0.83		0.35		0.77	
Breastfeeding[d]	Never	125,722	26	1.00 (reference)	1.00 (reference)[e]	8	1.00 (reference)[e]	18	1.00 (reference)[e]	0.23
	Ever	831,570	131	0.60 (0.39–0.92)	0.63 (0.40–0.97)	26	1.15 (0.43–3.05)	105	0.52 (0.31–0.89)	
Exogenous hormone use	Never use	887,175	140	1.00 (reference)	1.00 (reference)	31	1.00 (reference)	109	1.00 (reference)	0.24
	Ever use	141,407	27	1.44 (0.93–2.23)	1.45 (0.93–2.25)	4	0.72 (0.25–2.08)	23	1.75 (1.07–2.84)	
Age at menarche, y	≤13	316,896	25	1.00 (reference)	1.00 (reference)	5	1.00 (reference)	20	1.00 (reference)	0.19
	14–15	466,496	82	1.54 (0.95–2.50)	1.55 (0.96–2.51)	24	3.01 (1.13–8.05)	58	1.17 (0.67–2.02)	
	≥16	245,189	60	1.59 (0.95–2.66)	1.54 (0.92–2.60)	6	3.36 (0.99–11.4)	54	1.19 (0.68–2.10)	
	P_{trend}[f]		60	0.12	0.10		0.05		0.54	
Menopausal status	Pre-menopause	481,912	35	0.96 (0.58–1.59)	1.04 (0.63–1.73)					
	Natural menopause	452,624	116	1.00 (reference)	1.00 (reference)					
	Surgical menopause	94,046	16	0.88 (0.51–1.51)	0.85 (0.49–1.47)					

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas
[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use
[c] Adjustments as in footnote b except for parity
[d] Parous women only
[e] Additional adjustment for age at first birth and breastfeeding
[f] *P* value for linear trend across categories of variable

Table 3-9: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by accident according to age at menopause and total fertility years in the JPHC Study

Variable	Category	Person-years	Post-menopause		
			Cases	Model B1[a]	Model B2[b]
				HR (95%CI)	HR (95%CI)
Age at menopause, y	≤47	177,875	42	1.00 (reference)	1.00 (reference)
	48–50	210,330	45	0.78 (0.50–1.22)	0.73 (0.46–1.17)
	≥51	158,485	45	0.93 (0.59–1.45)	0.87 (0.54–1.40)
	P_{trend}[c]			0.77	0.65
Total fertility span, y	≤32	204,419	51	1.00 (reference)	1.00 (reference)[d]
	33–35	167,339	34	0.72 (0.46–1.14)	0.70 (0.43–1.13)
	≥36	174,911	47	0.90 (0.59–1.36)	0.88 (0.55–1.42)
	P_{trend}[c]			0.60	0.62

[a] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas
[b] Based on model B1 and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status, and exogenous hormone use
[c] *P* value for linear trend across categories of variable
[d] Adjustments as in footnote b except for age at menarche

3.2.5. Sensitivity analyses

Compared with complete-case analyses, estimations derived from multiple imputations did not change substantially in terms of the magnitude or direction of the association between all reproductive factors and mortality risks of all external causes, suicide, and accidents (Tables 3-10 and 3-11). One exception was the association between accidents and breastfeeding. Regardless of increased sample size, this inverse association became null [0.75 (95%CI: 0.50–1.14)].

Table 3-10: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by all external causes, suicide, and accidents associated with reproductive factors using multiply imputed datasets in the JPHC Study

Variable	Category	Person–years[a]	All external causes		Suicide		Accidents	
			Cases[a]	HR (95%CI)[b]	Cases[a]	HR (95%CI)[b]	Cases[a]	HR (95%CI)[b]
Parous	No	85,453	35	1.00 (reference)[c]	20	1.00 (reference)[c]	12	1.00 (reference)[c]
	Yes	1,161,489	410	0.76 (0.55–1.10)	174	0.60 (0.38–0.95)	193	1.14 (0.64–2.01)
Parity[d]	1	94,819	40	1.04 (0.72–1.51)	20	1.12 (0.64–1.94)	15	0.88 (0.50–1.56)
	2	440,845	145	1.00 (reference)[e]	72	1.00 (reference)[e]	67	1.00 (reference)[e]
	3	351,076	128	0.79 (0.60–1.03)	50	0.66 (0.42–1.01)	65	0.89 (0.61–1.31)
	≥4	276,870	97	0.98 (0.72–1.33)	32	0.53 (0.53–1.41)	56	1.10 (0.73–1.66)
	P_{trend}[f]		35	0.51		0.20		0.56
Age at first birth, y[d]	≤22	264,701	86	1.00 (reference)[e]	38	1.00 (reference)[e]	43	1.00 (reference)[e]
	23–26	587,544	222	0.99 (0.75–1.20)	95	0.93 (0.62–1.39)	109	1.05 (0.72–1.51)
	≥27	309,245	102	1.10 (0.80–1.50)	41	0.90 (0.57–1.42)	50	1.22 (0.79–1.89)
	P_{trend}[f]		35	0.55		0.65		0.34
Breastfeeding[d]	Never	151,844	69	1.00 (reference)[e]	28	1.00 (reference)[e]	35	1.00 (reference)[e]
	Ever	1,009,647	341	0.70 (0.53–0.93)	146	0.73 (0.47–1.16)	167	0.75 (0.50–1.14)
Exogenous hormone use	Never use	358,704	78	1.00 (reference)	172	1.00 (reference)	185	1.00 (reference)
	Ever use	556,235	227	1.03 (0.75–1.42)	22	0.85 (0.54–1.36)	29	1.24 (0.81–1.89)
Age at menarche, y	≤13	332,005	140	1.00 (reference)	39	1.00 (reference)		1.00 (reference)
	14–15		35	1.14 (1.05–1.78)	106	1.52 (1.03–2.22)	33	1.19 (0.80–1.78)
	≥16	1,077,325	391	1.17 (0.86–1.59)	49	1.22 (0.77–1.94)	100	1.14 (0.74–1.76)
	P_{trend}[f]	169,619	54	0.31		0.39	81	0.55

[a] Calculations for person-years and the number of cases across categories were based on pooled estimates from all imputed dataset.
[b] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status and exogenous hormone use using multiple imputed datasets. Multiple imputations by the chained equations approach with 20 iterations were performed to impute missing values by including all covariates, person-years, and vital status. Estimations were then combined using Rubin's rules (the STATA mi procedure). Estimations were restricted to parous women for breastfeeding and age at first birth, and to postmenopausal women for age at menopause and total fertility years.
[c] Adjustments as in footnote b except for parity
[d] Parous women only
[e] Additional adjustment for age at first birth and breastfeeding
[f] *P* value for linear trend across categories of variable

Table 3-11: Hazard ratios (HRs) and 95% confidence intervals (CIs) of death by all external causes, suicide, and accidents associated with menopausal status, age at menopause and total fertility span using multiply imputed datasets in the JPHC Study

Variable	Category	Person–years[a]	All external causes		Suicide		Accidents	
			Cases[a]	HR (95%CI)[b]	Cases[a]	HR (95%CI)[b]	Cases[a]	HR (95%CI)[b]
Menopausal status	Pre-menopause	481,912	113	0.90 (0.67–1.19)	72	1.08 (0.70–1.68)	36	0.92 (0.58–1.46)
	Natural menopause	452,624	287	1.00 (reference)	105	1.00 (reference)	155	1.00 (reference)
	Surgical menopause	94,046	43	0.88 (0.63–1.23)	17	0.99 (0.56–1.77)	22	0.93 (0.59–1.46)
Age at menopause, y[c]	≤47	234,944	99	1.00 (reference)	32	1.00 (reference)		1.00 (reference)
	48–50	279,204	142	0.94 (0.70–1.26)	65	1.14 (0.68–1.59)	55	0.78 (0.52–1.16)
	≥51	202,936	89	0.87 (0.64–1.19)	27	0.82 (0.48–1.38)	69	0.87 (0.57–1.32)
	P_{trend}[d]		102	0.38		0.55	53	0.56
Total fertility span, y[c]	≤32	278,611	95	1.00 (reference)[e]	38	1.00 (reference)[e]	55	1.00 (reference)[e]
	33–35	213,780	160	0.87 (0.64–1.17)	51	1.06 (0.65–1.73)	77	0.72 (0.48–1.07)
	≥36	218,693	75	0.95 (0.67–1.35)	35	0.93 (0.58–1.50)	45	0.97 (0.60–1.56)
	P_{trend}[d]		78	0.75		0.81		0.83

[a] Calculations for person-years and the number of cases across categories were based on pooled estimates from all imputed dataset.

[b] Cox proportional hazards models (using attained age as time scale) stratified by 11 public health center areas and adjusted for BMI, smoking habit, alcohol consumption, perceived stress level, living with a spouse and history of diseases, parity, age at menarche, menopausal status and exogenous hormone use using multiple imputed datasets. Multiple imputations by the chained equations approach with 20 iterations were performed to impute missing values by including all covariates, person-years, and vital status. Estimations were then combined using Rubin's rules (the STATA mi procedure). Estimations were restricted to parous women for breastfeeding and age at first birth, and to postmenopausal women for age at menopause and total fertility years.

[c] Post-menopausal women only

[d] *P* value for linear trend across categories of variable

[e] Adjustments as in footnote except for age at menarche

3.3. Summary of findings

Based on a large-scale population-based cohort study with 1,028,583 person-years, our results support the important roles of parity and breastfeeding in the risk of all-cause and major causes of external deaths. Age at menarche and exogenous hormone use were associated with death by all injuries or accidents. Age at menarche and exogenous hormone use were also potential makers for injury. Suicide and accidents accounted for 45% and 51% of external causes of death, respectively, and thus estimations of all external causes were similar to those for suicide or accidents. Our data also showed null associations between mortality risk by external causes and several reproductive factors, including age at first birth, menopausal status, age at menopause, and years of fertility.

4. DISCUSSION

4.1. Summary of findings

In this large-scale and well-designed prospective cohort study, reproductive factors were explored as possible markers for the risk of mortality among women. To my knowledge, this is the first large-scale study to investigate the association between comprehensive reproductive factors and risk of all-cause and cause-specific mortality including external causes in Japanese women. A novel finding of this study was the association between breastfeeding and external cause of death. This investigation has not been reported elsewhere. The data also revealed null associations between several reproductive factors and each cause of death: these findings are also meaningful in understanding the underlying mechanism.

4.2. Study contributions and potential mechanisms

4.2.1. Parity

The reduced risk from all-cause mortality in parous women versus nulliparous is consistent with previous studies, including a systematic review and meta-analysis [50, 53-55]. In terms of major causes of death, findings of inverse associations between parous women and mortality risks from total cancer, breast cancer, ovarian cancer, heart disease, and cerebrovascular disease were similar to those of previous studies [50, 55, 57]. Together, the lower risk of all-cause mortality in women with two or three births is partly consistent with previous reports that have shown a U- or J-shaped association between the number of births and mortality risk [52, 55, 56]. The consistencies were seen for the association between the number of births and cause-specific mortality, total cancer, breast cancer, ovarian cancer, heart disease and cerebrovascular disease [50, 55, 57], but not all [48, 49]. The results from the secondary analysis did not change substantially, except for those of multiple imputations, which showed significantly lower mortality risks from all-cause and cancer in four or more births compared to single birth. Because subjects with missing data reported high parity on average compared to those with complete data, the increased sample size in the high parity group may have resulted in a change towards a significant association for mortality risk.

Approximately 50% of total mortality was attributable to total cancer, heart disease, and stroke in this study, which may be responsible for the major effect of parity on total mortality. It is well-known that increasing parity is associated with lower risk of developing breast and ovarian cancers through anovulation and the suppressed secretion of pituitary gonadotropins during pregnancy [36]. The lack of

a linear association of parity with mortality risk of all-cause and total cancer may be explained by various negative effects of the biological response to repeated pregnancy, namely susceptibility to diabetes, induction of hypertensive changes and increased body weight [126], although BMI didn't modify the effect of parity on mortality in this study. Early studies yielded inconsistent findings regarding the association between parity and circulatory disease [49, 55, 57, 63, 127]. Increasing parity was associated with higher risk of circulatory-disease events [49, 126, 128, 129], while several studies suggested ever parity as a protective factor against this mortality risk [55, 63]. The low mortality risk of circulatory disease with ever parity may be due to positive behavioral changes because of pregnancy, which lead to an increase in health consciousness [53].

To date, the biological mechanisms of the effect of parity in mortality are not fully understood. It is possible that nulliparity was a consequence of poor health status that prevented pregnancy or completed parity [55]. One suggested explanation is social and psychological changes due to parenthood, which possibly leads to healthy lifestyle choices and increased well-being [130]. A similar U-shape association between the number of children and all-cause mortality in men might supports this hypothesis [53, 57, 130]. The lack of a linear trend for mortality in men may also reflect the negative influence of low socioeconomic status in the high parity group [53]. The impact of the protective effects of having children was much stronger in women than men, suggesting pregnancy-related changes may mediate the risk of mortality [53]. However, there is not enough information to discern the physiological and psychological effects of pregnancy on mortality risk.

The decreased risk of suicide in women with ever parity was consistent with previous studies

regardless of marital status [76, 78]. A negative influence of being single (never married, separated, divorced, or widowed) is commonly quoted as a risk factor for suicide, but its impact is not much stronger in women than men [131, 132]. Parenthood has an essential role in protecting from suicide [71], and this effect may be much stronger when children are young [74]. Motherhood itself may contribute to protecting against suicide for women by inculcating a feeling of responsibility and self-worth, enhancing the social network and providing a positive social role [75, 130]. The presence of a child may play a significant role in a decision not to commit suicide, especially while the child is dependent [75] Older women tend to count on their adult children more than their spouse for help in difficulties with daily life [133]. As the main reason for suicide among Japanese women is physical and mental illness [134], an adult child may confer significant emotional and material support for parents in late life.

In this study, three births were associated with the lowest risk of suicide among parous women, while previous studies suggested an association between risk of suicide and increasing parity [75], high parity [79] or no clear pattern [78]. The lack of a linear trend in this study may be due to the adverse effect of a large family. This possibly imposes excessive burden from physical and mental stress and economic strain on parents [48, 54]. A selection effect might also explain the association between parity and mortality [57]. Women who are single because they never married or were divorced or widowed might have been aggregated to the never/low parity group. A poor health status that prevents women from becoming pregnant or completing a pregnancy, or psychiatric illness, may influence the decision to marry and have more children. For most studies, however, the reason for childlessness is unknown. The main reason for nulliparous was being single, or infertility, but childlessness by choice is becoming common in developed countries [135, 136].

The inconsistency seen in parity–related associations may be, in part, derived from variations in the definition, distribution and categorization of parity across studies. Accordingly, any comparisons should be made with caution; for example, whether stillbirths were included in the number of births, and whether nulliparous was included in models for the dose-responsiveness of parity. The categorization of parity in relatively old cohort studies (1, 2-4, 5-9, or ≥10 births)[48, 49] may not be applicable to recent birth cohorts. Nevertheless, as shown in Figure 4-1, an average or moderate number of births was the lowest risk group for all-cause mortality in most studies.

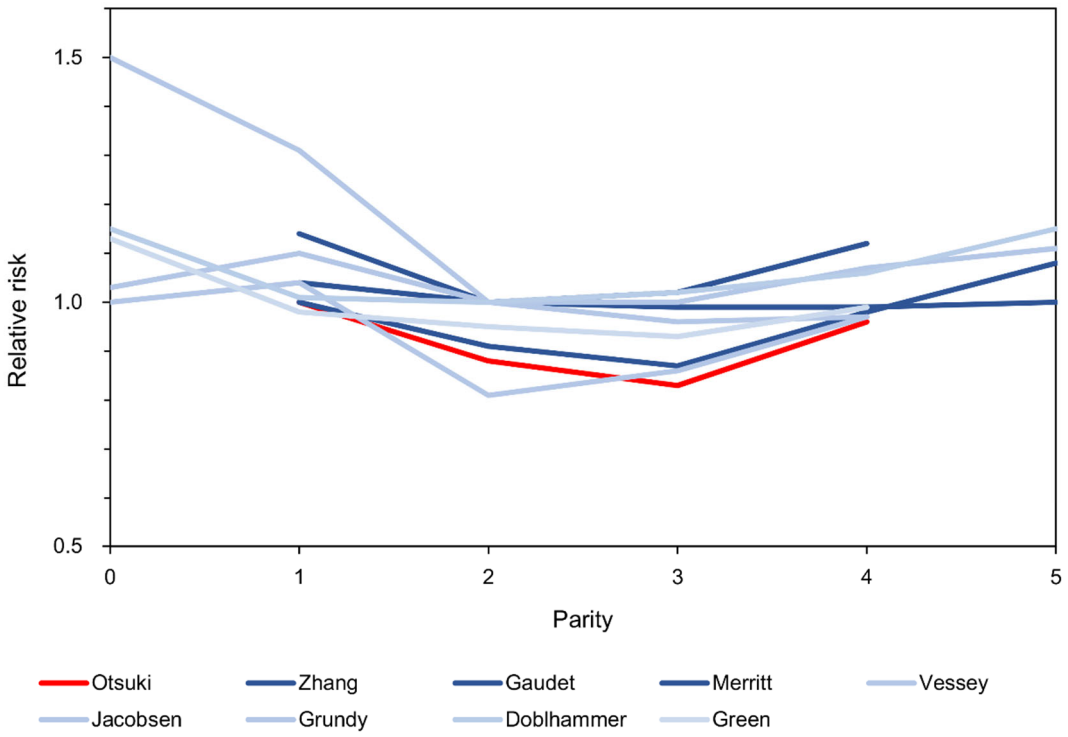


Figure 4-1: Comparison of relative risks for parity associated with all-cause mortality between this study and previous studies

Fertility patterns in the world have changed dramatically over past decades and an average number of children would shift toward downward trend (Figure 4-2)[1]. The large total fertility rate differences between 1960 and 1980, were much smaller as of 2016. Since 1980s, all selected countries experienced less than 3.0 average total fertility rate. Japan has experienced relatively lower total fertility rate than other selected countries for decades. As a country develops, the total fertility rate declines, resulting in a global average total fertility rate of 2.5 children per woman [137]. Parity for the lowest risk of mortality may change in next generations as the world continues to develop.

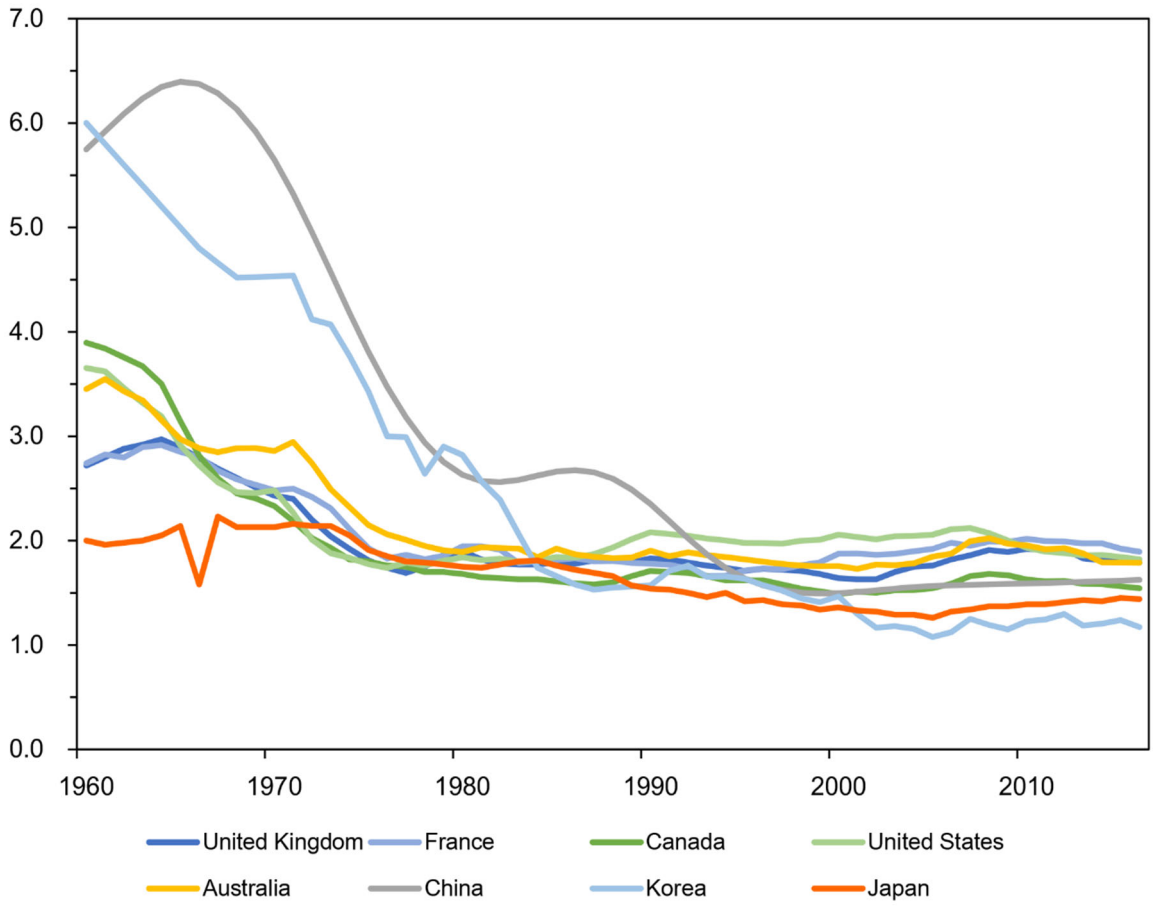


Figure 4-2: Total fertility rate in selected countries, 1960-2016
Source: The World Bank, 2018 [1]

4.2.2. Age at first birth

Among parous women, late age at first birth (aged more than 30 years) was associated with a higher risk of all-cause mortality compared to early childbearing (age less than 22 years). The substantially increased risk of breast cancer may be responsible for the marginally significant association between late age at first birth and total mortality. It is well-established that late pregnancy increases the development of breast cancer through the delayed final maturation of mammary cells [36].

However, the association between late age at first birth and mortality has been inconsistent in past studies [50, 55, 57, 58]. Adolescent pregnancy was associated with high risk of all-cause mortality [50, 55, 57], suggesting that low education level in women with early pregnancy is a distal risk factor related to higher mortality [58].

Globally, the mean age at first birth has dramatically increased in the last two decades as the country develops [138]. Japan has experienced relatively delayed age at first birth over the past decades compared to other selected countries shown in Figure 4-3.

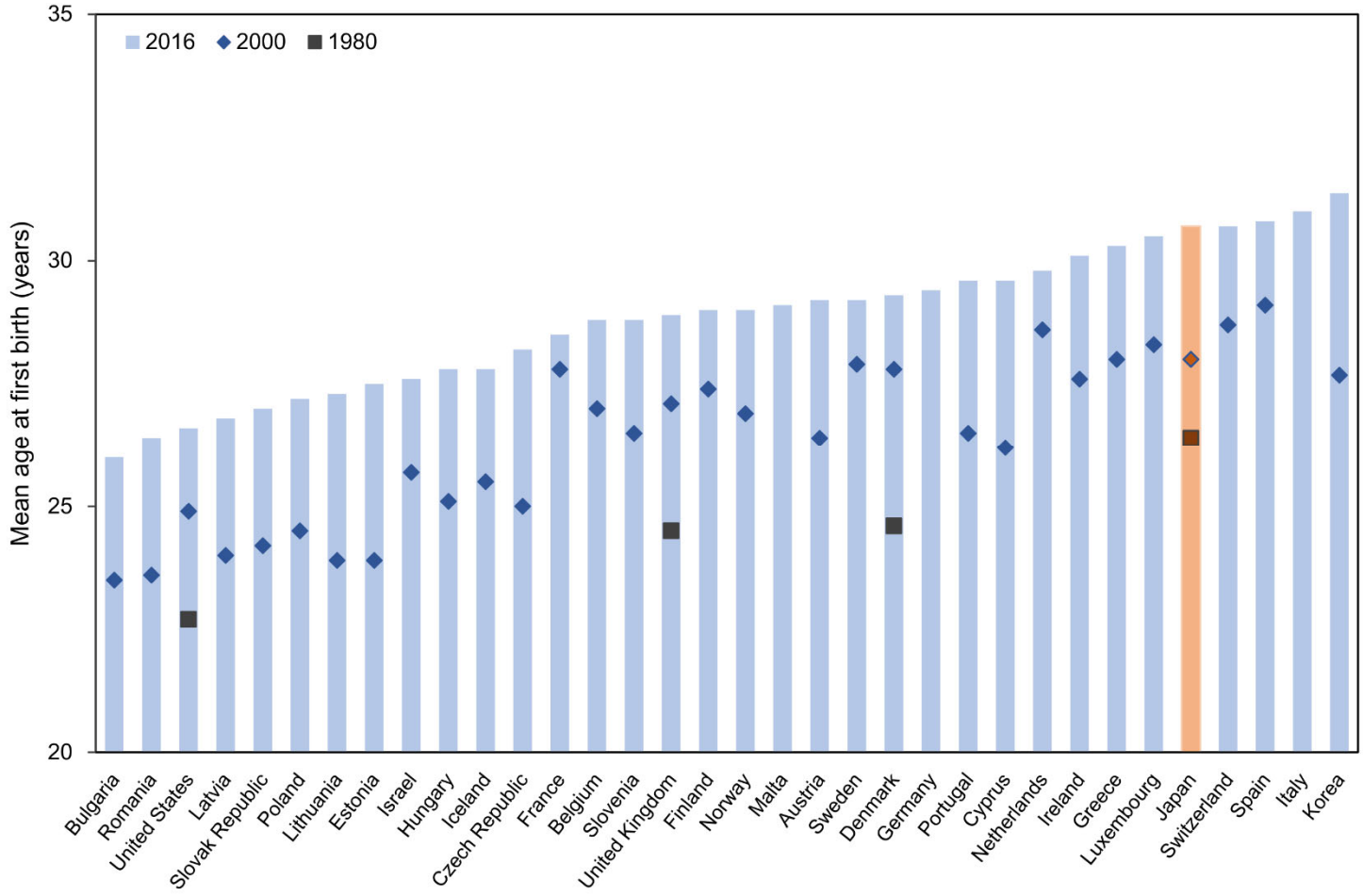


Figure 4-3: Mean age at first birth in selected countries in 1980, 2000, and 2016

Source: The World Bank, 2018 [1]

In Japan, the mean age at first birth has continued to increase for decades and reached 30 years old in 2010 (Figure 4-4)[41]. The delays in childbearing are considered to be a consequence of increases in women's education and participation in the workplace [138]. Late pregnancy and fertility decline accelerated after the second baby boom around 1970 with parallel rapid economic growth. The increased availability of abortion and dissemination of contraceptive information may also have spurred the decline [139, 140]. Therefore, women with high socioeconomic status might be categorized into group of later age at first birth, who may be prone to being more health-conscious compared to low socioeconomic status women. Given that socioeconomic status may be an important determinant of the timing of childbearing, biological mechanisms may be insufficient to explain the whole relationship between age at first birth and mortality risk [58].

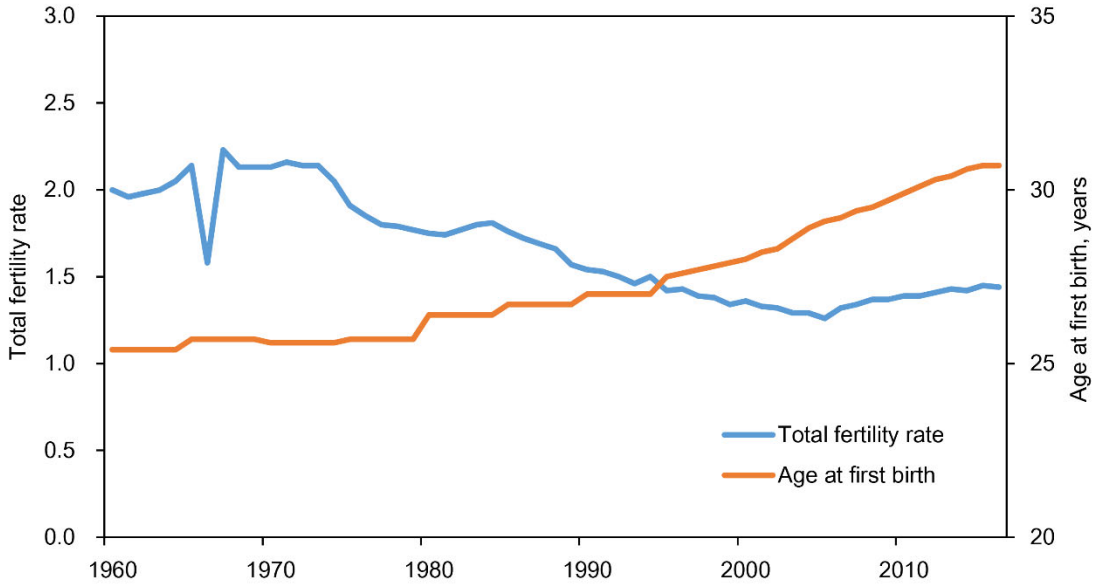


Figure 4-4: Trends in total fertility rate and age at first birth: Japan, 1960-2016.
The sharp drop in 1966 is explained by its being the year of the "Hinoeuma" superstition, in which many women wish to avoid bearing a girl.

Source: The Vital Statistics in Japan. Ministry of Health, Labour and Welfare, 2017[41]

4.2.3. Breastfeeding

Although there is growing body of evidence that breastfeeding has short- and long-term benefits against cardiovascular disease in women [141, 142], only limited studies have assessed its impact on mortality. Consistent with previous studies [55, 143], the experience of breastfeeding among parous women conferred a substantial risk reduction for mortality. Previous literature has shown that oxytocin, which plays a major role in lactation, and lactation itself offer broad protection against cerebrovascular disease by preventing high blood pressure, natriuresis, diabetes, and by mobilizing accumulated fat stores during pregnancy [141, 144]. The lactating child is also considered to protect against estrogen-responsive cancers through the decreased exposure to estrogen with missed menstrual cycles during lactation [145], although data of this study did not provide a significant association between breastfeeding and breast cancer mortality.

Ever breastfeeding was inversely associated with mortality risk from all external causes and accidents. In particular, a much lower risk of accidents was seen among postmenopausal women. Because no previous literature has investigated the association between breastfeeding and external causes of death, an explanation for these associations is unknown. One possible pathway is the protective effect of breastfeeding on several diseases after menopause including cancer, hypertension, diabetes, hyperlipidemia, and cardiovascular disease [141, 145]. These are likely to increase the risk of external cause of death [112, 146, 147]. Another possible explanation is the protective effect of breastfeeding on osteoporosis and subsequent fracture occurrence [148, 149], and Alzheimer disease [150], although these associations remain inconclusive. However, because the association became insignificant after imputations regardless of increased sample size, this finding should be interpreted with care.

Similar to the case with parity, a specific reason for never experience of breastfeeding was not available in most studies. According to statistics for infant nutrition in Japan, the percentage of exclusive breastfeeding at one month after birth decreased from 67.8% in 1960 to 31.7% in 1970, and the rate of artificial formula use rapidly increased in 1970 [151]. The major reason for using artificial formula was perceived insufficient breast milk (79.7%), followed by return to work (16.7%), supplement for breast milk (6.5%), and health condition (6.0%)[151]. Smoking status, low birth weight of child, and perceived insufficient breast milk supply were negative factors on breastfeeding duration in Japan [152].

Regarding the global trend of mothers' breastfeeding behaviors, attitudes toward breastfeeding were different by income levels [153]. Ever and continued breastfeeding was more common in low than high income countries. A previous literature reported that prevalence of indicators, including ever breastfed, exclusive breastfeeding and continued breastfeeding, decreased with increasing national wealth [153]. Breastfeeding is a positive health behavior in low- and middle- income countries, however as income increases there may be a shift towards breastmilk substitutes. Barriers and determinants to influence a woman's decision to breastfeed include work-related issues[154], perceived insufficient breast milk[155], personal preferences, [156], physical/ medical problems [154, 156], socio-economic status[12], age[155], marital status[157], maternal smoking[155], and support from medical staff or specialist[155, 158].

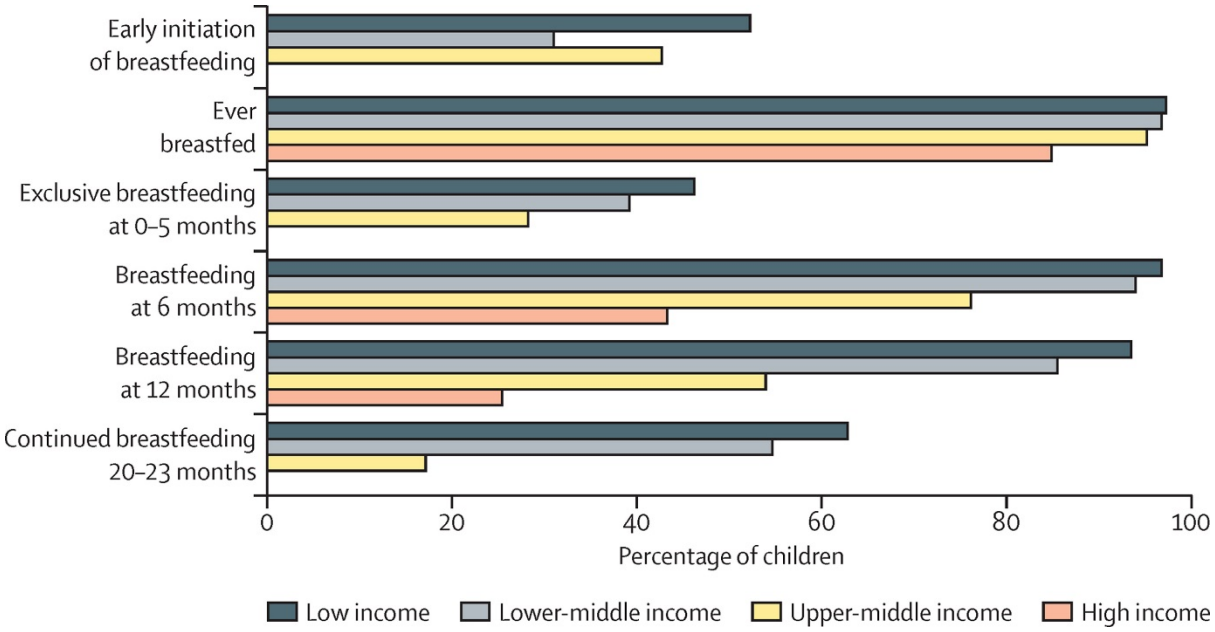


Figure 4-5: Breastfeeding indicators by country income group, 2010
Source: CG Victoria et al. *Lancet*. 2016 [153]

One of the major limitation of this study was lack of assessment of the dose-response relationship between breastfeeding and mortality risk. Although there is no clear pattern for the intensity and duration of lactation against risk of specific diseases [55], a long lifetime duration of lactation was inversely associated with several cardiovascular risk factors and deaths [142]. The lack of detailed information on breastfeeding, such as frequency and duration, requires further investigation to confirm this intriguing association between breastfeeding and the risk of death.

4.2.4. Age at menarche

Although the majority of studies reported inverse associations between later age at menarche and mortality risk from all-cause, total cancer, circulatory disease and stroke [55, 59-62], this study contradicted these findings. Proposed pathways were early exposure to various endogenous hormones, including sex steroids and growth hormones [159]. There is accumulating evidence that early onset at menarche was associated with higher adult BMI [160], development of breast cancer, morbidity of CVD-related events such as high blood pressure and glucose intolerance [159], and risk-taking behavior such as early alcohol drinking and smoking [161].

Regarding mortality risk from injuries, the marginal positive associations between late age at menarche and risk of all injuries and accidents may be explained by risk of cognitive impairment [162, 163] or osteoporosis [164, 165] in later life. The delayed initiation of secreting gonadal sex steroid influences musculoskeletal function [166]. Estrogen plays a positive role in regulating neuronal biochemistry and cognitive function [167]. However, evidence from epidemiological studies on the association between early and/ or long exposure to estrogen and cognitive function remains inconclusive [162, 163, 168].

As the onset of menarche was earlier in women born in the 1950s than in the 1930s (mean age of menarche at 13.6 versus 15.7 years old) in this study, another explanation may be selection bias: older subjects were aggregated to the group of late age at menarche. As such, the increased risk of mortality in women of late age at menarche might be simply explained by aging rather than the timing of the

onset of menarche. A similar tendency is shown in Figure 4-3 and was reported in a previous Japanese study, which suggested that the improved nutrition and environment, and progress in socioeconomic conditions following World War II may have affected the varying distribution of menarcheal age among Japanese women [169].

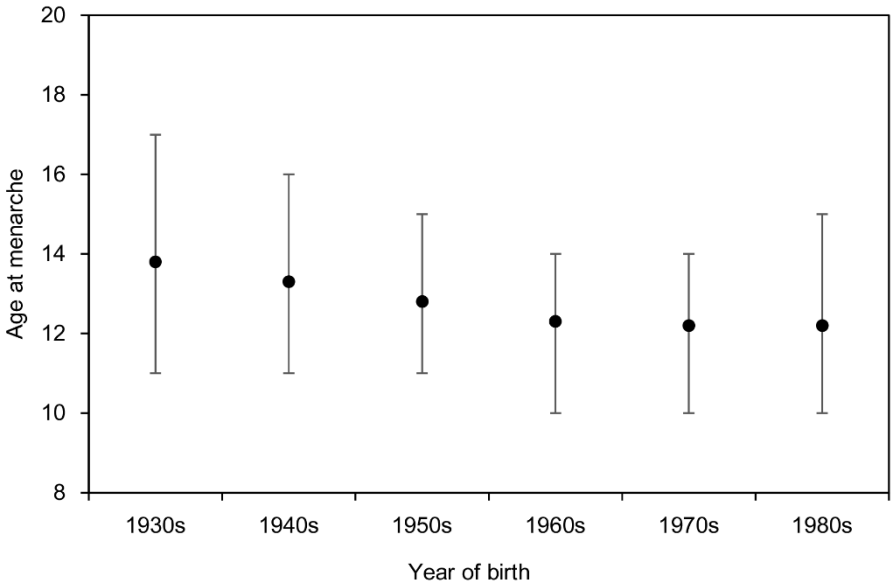


Figure 4-6: Secular changes in mean age at menarche for women born between 1930 and 1985

Whiskers: 95% confidence interval

Source: Hosokawa (2012) [169]

A previous paper, which summarized mean age at menarche in 67 countries, reported geographical differences in age at menarche (Figure 4-8) [170]. Early age at menarche appears to occur in countries where the life expectancy and Gross Domestic Product is high.[171]. Japan was grouped in the earliest age at menarche globally. The beginning of reproductive capacity in women is associated with both biological factors, i.e., genetic variability, and environmental factors, i.e., health and socioeconomic conditions[171]. Especially, poor fat accumulation due to poor nutrition and excessive physical activities, i.e., athletic women and child labor, is a well-known factor delaying the onset of menarche [170]. Accordingly, onset of menarche may be partly influenced by situations where women are born and live.

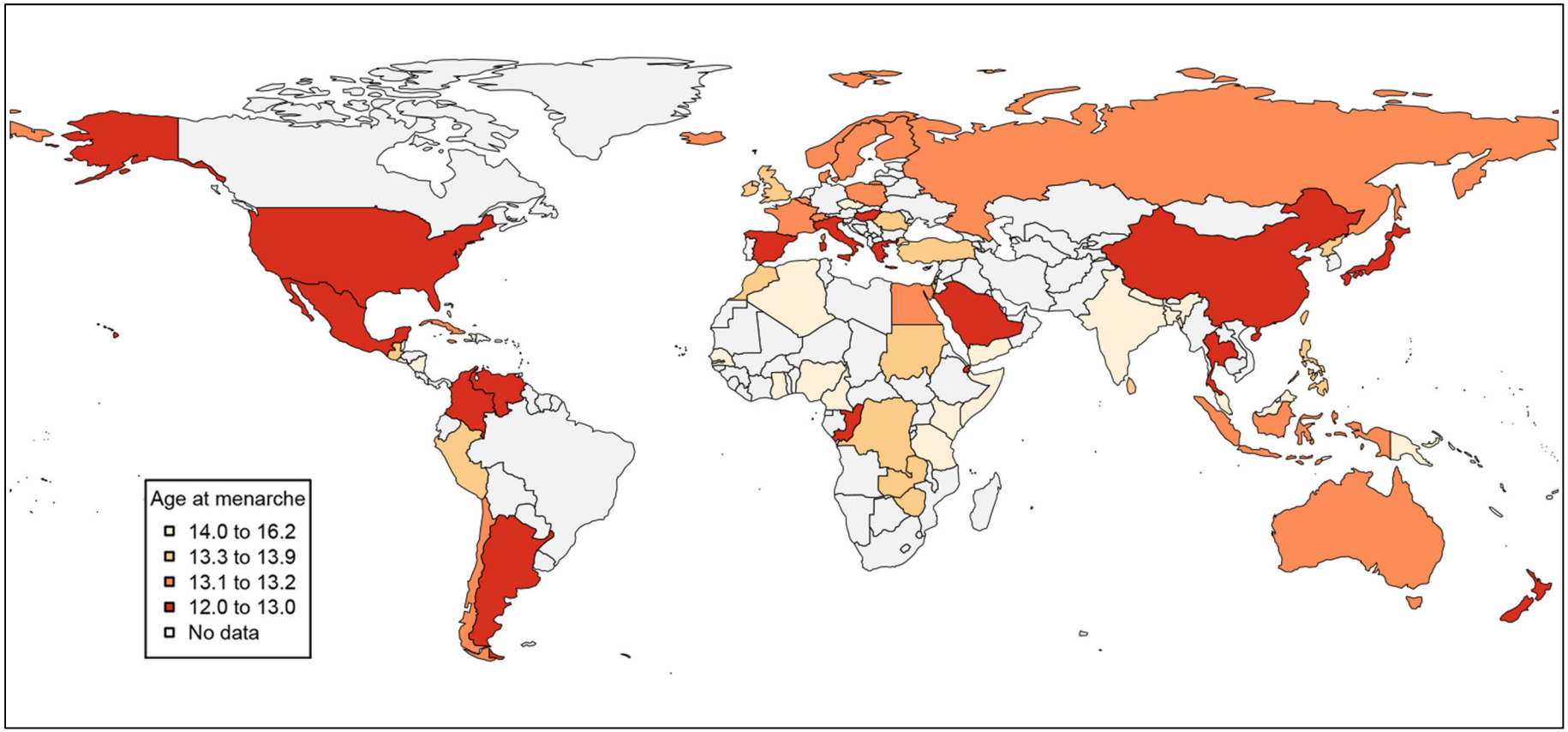


Figure 4-7: Mean age at menarche by country, 2001
Source: Thomas et al. 2001[171]

4.2.5. Menstrual cycle

Few studies have examined the association between menstrual cycle length and risk of mortality [172]. This study suggests that a longer menstrual cycle is associated with a strongly decreased risk of respiratory disease mortality, but conversely also an increased mortality risk from cerebrovascular disease. Given that variability in menstrual cycle length is attributable to follicular phase length, particularly rising estradiol levels, women with long cycle length experience fewer cycles and less time spent in the luteal phase [119, 173-175]. A longer cycle length is also associated with relatively low concentrations of estrogens, which may result in low cumulative exposure to estrogens during reproductive age period. As such, lower exposure to estrogens, which has cardioprotective effects, may explain the positive association between longer menstrual cycle and risk of cerebrovascular disease [176]. While the association between length of menstrual cycle and the mortality risk of cerebrovascular disease was statistically significant, a similar result was not seen in the risk of heart disease, which may partly share the mechanism with cerebrovascular disease. One possible reason for this is combining subgroups of heart disease which may have attenuated the result toward null.

Regarding respiratory disease, the prevalence of non-allergic asthma is higher in women than men, and respiratory symptoms fluctuate over the course of the menstrual cycle [177, 178]. As such, a complex interplay among sex hormones may be the underlying mechanism to explain the association between reduced risk from respiratory disease and long menstrual cycle length [173]. Women with a long length of cycle may be relatively less exposed to progestin, which dominates during the luteal phase. Given that progestin has the airway inflammatory effects, a reduced risk of respiratory disease may arise

from less inflammatory conditions during reproductive age period among women with a long cycle [119, 175].

As of 2018, there is no report on international comparisons regarding length of menstrual cycle. Some reports compared the variety of menstrual cycle and the concentrations of female sex steroid during reproductive age. Asian women had a significantly longer mean cycle length[179] and estrogen levels were higher in African-American women[180] compared with Caucasian women. These racial differences in menstrual-related factors may be partly explained by environmental determinants as well as genetic heterogeneity [180]. Environmental factors which influence menstrual function include psychological stress[181], caffeine consumption[182], smoking[183], alcohol consumption and physical activity[179]. Ageing is negatively associated with cycle length because of shortening of the follicular phase . Accordingly, it is doubtful that the length of menstrual cycle is consistent throughout the reproductive span. Results for the length of menstrual cycle should be interpreted with caution due to the possibility of misclassification and biased estimations.

4.2.6. Exogenous hormone use

In women with exogenous hormone use, no association with risk of all-cause or cause-specific mortality was observed. Several studies showed inverse associations between ever user of OCs and mortality risk for all-cause and cause-specific mortality [56, 65, 128]. The positive associations between external cause of death and women with ever user of OCs has been reported, [64, 65, 81] whereas there is controversy remains with regard to hormone therapy use [184, 185]. This study showed a marginally increased risk of accidents among ever users of exogenous hormone. Nevertheless, despite a potential

link between exogenous hormone use and risk of injuries, earlier studies did not provide potential biological mechanisms through which exogenous hormone use modulate the risk of injuries.

The lack of statistical significance may be due to the low prevalence of hormone use in this study population (13.4%) compared with Western studies [139, 186]. In addition, findings of this study for exogenous hormone use should be interpreted with care because of the combined effects of OCs and HT. The unavailability of detailed information on exogenous hormone use limited the ability to assess the effects of OCs and HT separately, and to compare this study's findings with those of other studies. Furthermore, the substantial change in exogenous hormone availability and pattern of use over the years prevents comparisons of associations with various exogenous hormones across studies.

A report from United Nations compared the global prevalence of OC use in 2015 (Figure 4-8)[187]. The prevalence of OC use in Japan was only 1.1% in 2015, which was similar to that of developing countries in South Asia and Africa. Between 2002 and 2010, the usage of menopausal hormone therapy sharply declined in European countries after the report from Women's Initiative trial due to fear of breast cancer risk [188]. Although the highest prevalence of total hormone therapy use was approximately 25% in Sweden, but its prevalence declined by about 8% in 2010.

The failure to obtain various information on exogenous hormone use in this study is due to the scarce usage of hormones at the time of recruitment. A survey in 1992 revealed that only 2.5% of women aged 45-64 and 1.3% of women of reproductive age reported current use of HT [189] or the high-dose OCs [190], respectively. Even after the legalization of oral contraceptives in 1999, the prevalence of

birth control pill usage has remained low compared to other developed countries [139, 191]. However, since randomized control trials of the Women's Health Initiative have failed to confirm the effect of hormone therapy on preventing coronary heart disease and hormone-related cancers (e.g., endometrial cancer and breast cancer) [186, 192], confirmation of the impact of this important factor should be addressed with care.

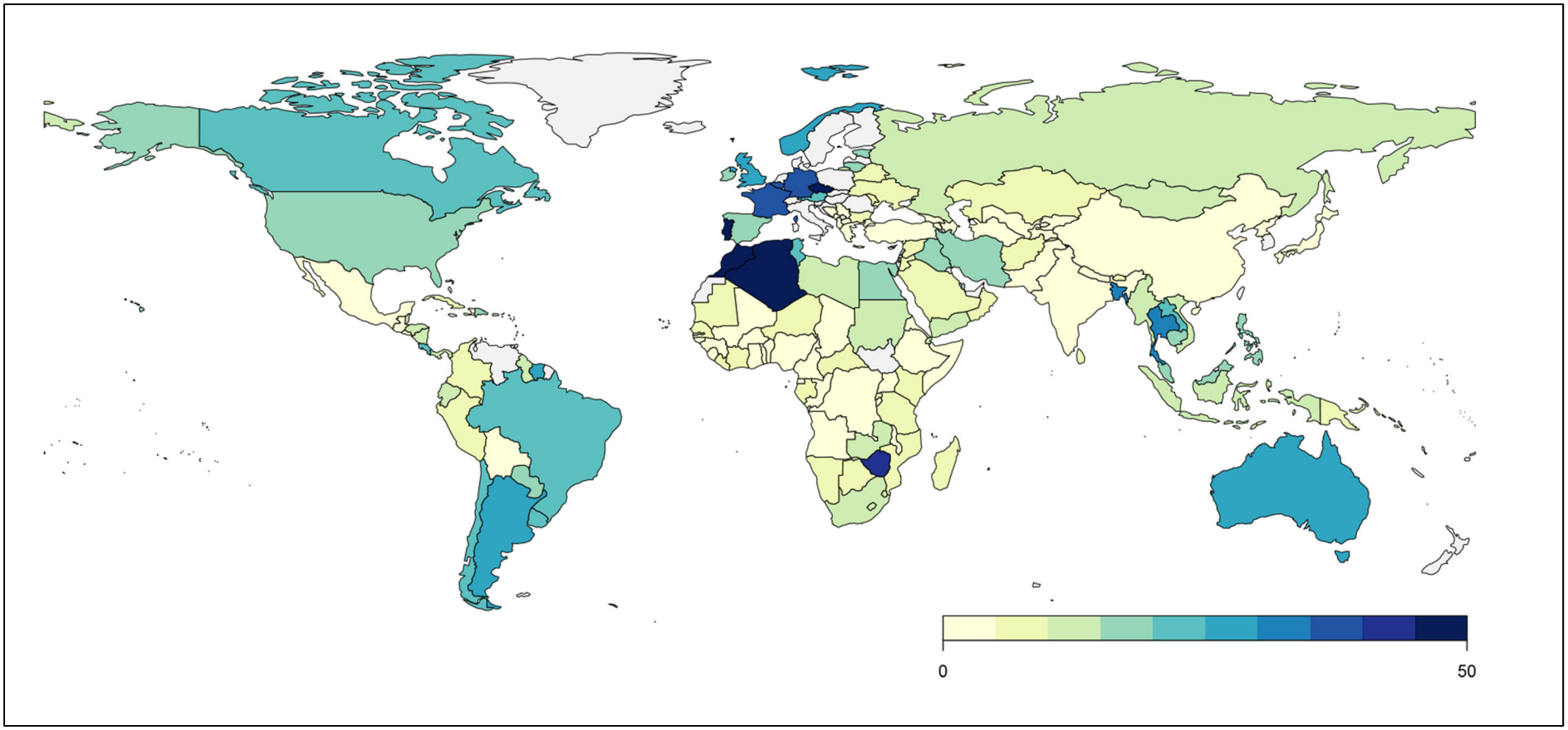


Figure 4-8: Prevalence of OC use in the world, 2015
Source: Trends in Contraceptive Use Worldwide 2015, United Nations, 2015[187]

4.2.7. Menopausal status, age at menopause, and total fertility years

Consistent with previous studies, older age at menopause was associated with lower risk of mortality from all-cause, cerebrovascular disease and respiratory disease [59, 193-196]. The association between late menopause and reduced cardiovascular disease risk is well established, because of longer exposure to estrogens [32, 59, 174, 176]. Endogenous estrogen has positive effects on lipid profile, namely preventing increases in cholesterol and triglyceride levels from increasing high-density lipoprotein cholesterol levels, and also preventing atherosclerotic plaque formation [39, 174, 176]. It appears reasonable that some protective effects against heart disease and cerebrovascular disease mortality were attenuated among post-menopausal women. However, in stratified analyses for post-menopausal women, overall estimations were not substantially changed compared to estimations yielded from whole subjects.

A decreased trend of respiratory disease risk in late age at menopause was consistent with previous finding [177]. The prevalence of respiratory symptoms and lower lung function were dominant in post-menopausal women compared to premenopausal women; this is because increased insulin resistance induces an inflammatory condition in postmenopausal women [197]. In addition, because estrogens partially protect the lung from airway fibrosis, a decreasing trend in mortality risk from respiratory disease may be associated with longer exposure to estrogen [177, 197].

Collectively, as may be expected, a longer fertility span was also associated with a lower risk of all-cause mortality. Decreased trends of mortality risk from heart disease, cerebrovascular disease, and respiratory disease were also observed. The possible mechanisms are similar to those of menopause; a

longer interval between menarche and menopause indicates a longer period of benefits from endogenous sex hormones. Given that the long exposure to sex steroids increases the development of estrogen-responsive cancers [59], null associations between menopause and total fertility years, and mortality from any cancers were contrary to expectations. One explanation is an increase in competition for risk of dying from other causes such as circulatory disease after menopause [198]. Among postmenopausal women, only 25% of mortality from breast cancer was identified, whereas 85.7% for heart disease and 79.0% for stroke occurred. Long exposure to estrogen could indeed increase the risk of breast cancer, yet the impact of circulatory disease may be much stronger in terms of mortality.

Interestingly, surgical menopausal women was associated with substantially reduced mortality risk from respiratory disease. As an experiment of animals which were had both ovary surgically removed have indicated [173], the dramatic decline in exposure to progestin is a potential pathway for decreased risk from respiratory disease in surgically menopausal women.

Regarding external causes of death, this study found null associations between suicide and age at menopause, fertility years and menopausal status. As the perimenopause phase is a particular risk for developing depression and higher suicidal behaviors [82], a high risk of suicide among premenopausal women were expected. In fact, suicide is the second cause of death among Japanese women aged 30-49 years old, and its rank drops as the age category rises [68]. Interactions between hormonal change and several stressful life events such as interpersonal problems and empty nest experience may lead women to be susceptible to mental illness and subsequent suicide behaviors [87, 199].

A systematic review and meta-analysis demonstrated geographical differences in age at natural menopause across six continents (Figure 4-9). Overall mean age at natural menopause was 48.78 years old. Age at natural menopause was generally lower among African, Latin American, Asian and Middle Eastern countries, and was higher in economically more developed regions including Europe, Australia and the USA. This study also reported that socioeconomic position contributed to the variation in onset of menopause; a dose response for later age at natural menopause, with increasing education or occupational level being associated with delayed age at natural menopause. Lifestyle-related factors including smoking and moderate or high physical activity were associated with early menopause. At least half of the interindividual variability in menopausal age appears to be attributable to genetic factors [200], indicating the rest may be explained other factors such as socioeconomic status and lifestyle. Therefore women with late age at natural menopause might have enjoyed a higher economic position or had a better lifestyle compared to early onset of menopause.

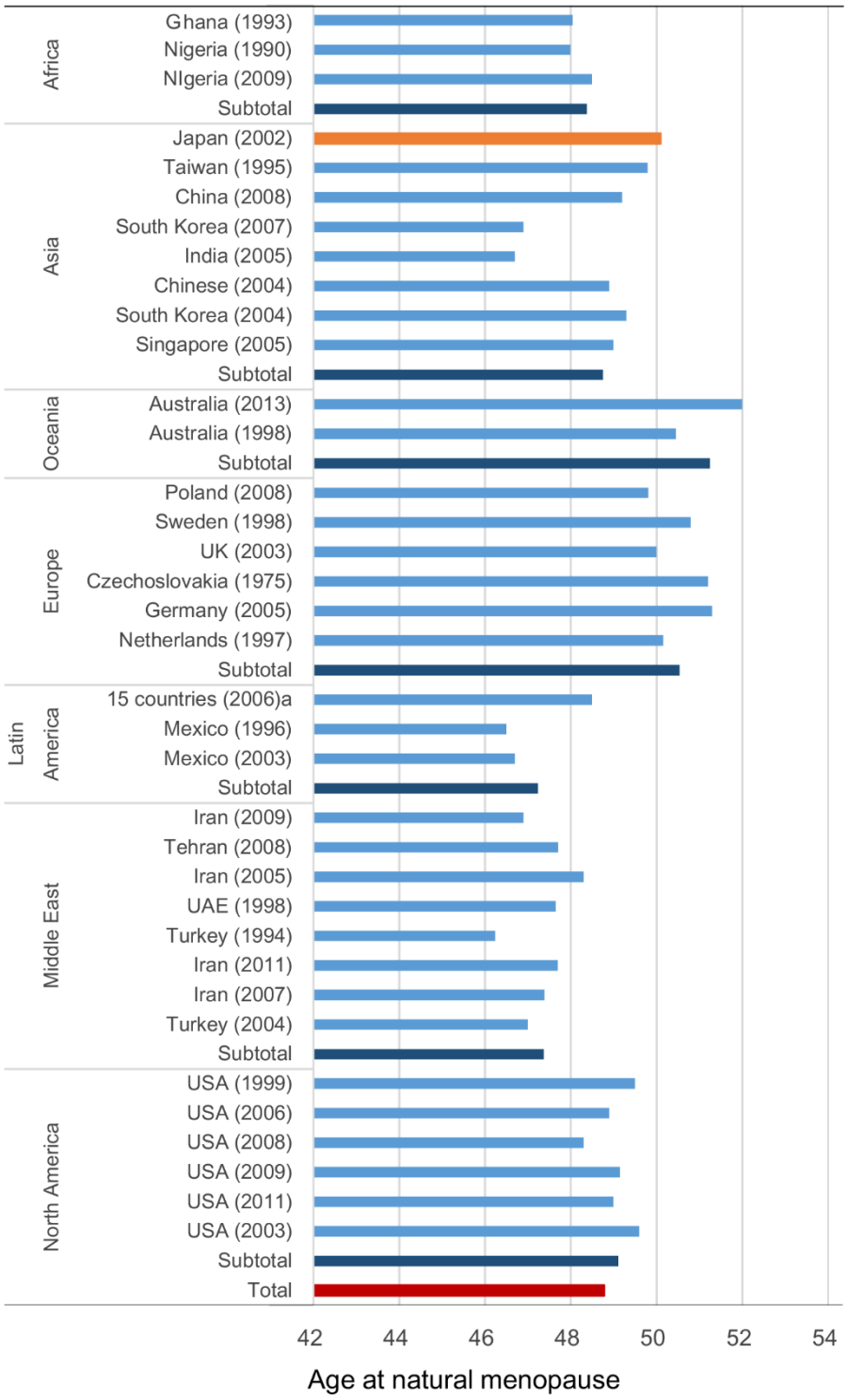


Figure 4-9: Mean age at natural menopause[b] in the world, 2014

[a]Study included centres from North, Central and South America in 15 countries (Argentina; Bolivia; Brazil; Chile; Colombia; Costa Rica; Cuba; Dominican Republic; Ecuador; Honduras; Mexico; Panama; Paraguay; Peru; Uruguay)

[b]The permanent cessation of menstruation resulting from the loss of ovarian follicular activity, occurring after 12 consecutive months of amenorrhea

Source: Schoenaker et al. 2014[201]

4.3. Strengths and limitations of the study

To my knowledge, this is the first large-scale prospective study to examine the impact of reproductive factors and risk from all-cause and cause-specific mortality including external cause among the Japanese population. Specifically, the possible association between breastfeeding and risk of external cause of death was a novel finding, which has not been investigated elsewhere. Study strengths include a large population-based sample with long follow-up period, its prospective design, high response rate (more than 80%) and low loss to follow-up. The availability of a variety of reproductive factors enabled a comprehensive assessment of the relationship between reproductive factors and external causes of death. Study participants consisted of a general population across Japan, likely making findings of this study generalizable to the entire population.

Another strength of this study is its reporting in accordance with the STROBE statement, a checklist of items that should be reported in articles of observational studies [98]. Previous observational research has often failed to report important information. Some studies did not specify key elements of the study design including the eligibility of criteria, median follow-up time and percentage of loss to follow-up. Few studies addressed the possibility of reverse causation; for example, they did not exclude or report participants with a history of diseases that influence the events. The rationale behind the selection of potential confounding variables was often not reported, and some studies failed to adjust for essential confounders, such as smoking status. Very few studies reported descriptive data of participants with missing data, or explained how they addressed missing data. Therefore, the quality and transparency of the present study meet the international standards compared with previous studies mentioned above.

Several limitations should also be raised. The main findings were obtained based on complete case analyses under the assumption of missing at random, which may have introduced selection bias. However, this issue was addressed by using the imputation approach to include all eligible study subjects. Although data of this study were large enough, some of the results of secondary analyses may be due to chance. Reproductive exposures were assessed once only at the time of the baseline survey. However, reproductive characteristics are unlikely to have changed among the study population, and additional sub analyses were conducted among only to menopausal women. Specific details of breastfeeding (i.e., duration and frequency) and use of exogenous hormones (i.e., formulation, dosage, and duration) were not available. Reproductive events that occurred long before may be subject to memory bias which may lead to misclassification and attenuate risk estimates towards null. It is also possible that age at menopause and menopausal status were misclassified, because these were determined by the self-report of subjects. The validity of recalled reproductive events decreased with increasing number of years since the events. Therefore, it is possible that reproductive events that occurred many years before and the report from older women may be subject to recall and memory bias.

Although relevant covariates were taken into account, data for possible other important confounders such as socioeconomic status and history of mental illness was not available. Reproductive behaviors are strongly associated with socioeconomic status, residual confounding between reproductive factors and outcomes could exist. Regarding causal pathways and the inter-relationships of variables with health outcomes, a causal framework was not generated because of uncertainty in causal inference

between variables, inclusion of many outcomes in and the possibility of other unknown residual confounders. Improper omission or inclusion of covariates may have lead to biased estimation [202]. Because physicians in Japan diagnosed sudden death or the death in the end stages as heart failure, the adoption of ICD-10 caused a decline in mortality rate from heart disease. Therefore, misclassification of mortality from heart disease may have occurred regarding deaths occurring before 1995 in the JPHC Study.

Injuries from huge disasters may have occurred regardless of potential risk factors. However, no external cause of deaths was identified among study subjects in corresponding areas of the major earthquake which struck Japan in 2011 from its occurrence until one month later. Lastly, because the study subjects were limited to Japanese only, results of this study may not be generalizable to other populations.

Given the strengths and limitations of this study, recommendations to improve future studies are listed as follows:

1) Additional details on breastfeeding and usage of exogenous hormone, negative outcomes of pregnancy such as spontaneous abortion, history of infertility, genes related to specific diseases, socioeconomic status, deprivation level, and marital status may improve the models and allow a better understanding of women's health from physiological, psychological and sociological perspectives. The duration of lactation and use of OCs enables calculation of the lifetime ovulatory period, which might be a more informative factor than the total reproductive years.
2) Linkage with several databases enables a variety of analyses regarding burden of disease because

limited incidence data was available in the JPHC Study. For example, a history of the disease in the national claims data will give further information on histories of other diseases, such as mental illness and diabetes mellitus. Particularly given that cognitive impairment has become the leading cause of death among women, linking the cohort study with a database of medical care for the elderly would help to elucidate how reproductive factors and lifestyle in middle age affect cognitive function and nursing care needs in later life.

5. Conclusion

My study supports an important role of reproductive factors in all-cause and major causes of death among Japanese women. In summary, lowered risks from all-cause and major causes of deaths were observed among parous women, and in women with two or three births, experience of breastfeeding, late age at menopause, and long fertility years. In contrast, late age at menarche or first birth were positively associated with mortality risk. Overall, both physiological and psychological changes with reproductive events may be partial pathways to determine the women's longevity. The varying results seen in the analyses for total and site-specific cancer imply that the carcinogenic effects of reproductive factors may differ among organs by the type and/or expression of hormone receptors. Several tissue-specific variations in hormone production and catabolism may cause differences in cumulative exposure to a hormone [36].

A key challenge is how to translate these findings into public health policy. I hope that this study provides a better understanding of how reproductive history influences long-term health, and help women in making informed choices and decision. The prolonged effect of lactation against mortality suggests the need for vigorous promotion of breastfeeding from the perspective of maternal health. Importantly, causes of death are never the consequence of a single cause; a combination of personal, cultural, social and biological features likely interact with fluctuations in sex hormones among women [84, 203, 204]. Although most reproductive factors are not modifiable, unlike lifestyle, these factors are common exposures in almost all women around the world. Women born at different periods have followed varying fertility pathways, played different roles in society, and have had different access to

modern medical technologies. As the distribution of reproductive factors varies with changes to the environment in which women live, continuous research is needed to ensure ongoing improvement to women's health.

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Appendix A: Ethical approval

（様式６-1）

2015年08月18日

研究倫理審査委員会結果通知書

国立研究開発法人国立がん研究センター理事長　殿

国立研究開発法人国立がん研究センター研究倫理審査委員会委員長

研究計画に関する申請あるいは報告について、当センターの手順書に基づき審査を行い、以下のとおり判定した。

研究課題番号	2001-021		
研究課題名	多目的コホート研究(JPHC Study)		
研究責任者	がん予防・検診研究センター　がん予防・検診研究センター　津金　昌一郎		
適用となる倫理指針	□人を対象とする医学系研究に関する倫理指針 □臨床研究に関する倫理指針　■疫学研究に関する倫理指針 □ヒトゲノム・遺伝子解析研究に関する倫理指針 □その他		
研究計画書等に関する情報	研究計画書の作成日：2015年06月25日　第2015/06/25版（バージョン） 説明同意文書の作成日：－　第－版（バージョン）		
申請/報告の種別	□研究計画の新規申請　■研究計画の変更申請 □実施状況報告　□安全性情報に関する報告 □研究に関する不適切事案に関する報告 □その他		
審査方法・判断方法	□通常（合議）審査（委員会開催日：　年　月　日） ■迅速審査（適用条件：委員会手順書第12条第1項第1号　軽微な変更） □研究倫理審査委員会委員長決裁 □あらかじめ指名する者による審査不要の判断※ □		
委員会判定日（上記※の場合を除く）	2015年08月18日	判定	■承認　□条件付き承認　□却下 □保留（継続審査）　□差し戻し □非該当　□その他
付帯条件・勧告			
判定が承認以外の場合の理由、その他の意見			
備考	審査対象文書：研究実施計画書・研究概要の情報公開原稿		

（様式６-2）

2015年08月18日

研究許可申請に関する指示・決定通知書

津金　昌一郎　殿

国立研究開発法人国立がん研究センター理事長

（押印省略）

貴殿から申請のあった上記の研究について、以下のとおり決定したので、通知する。

判定	■許可　□不許可　□差し戻し　□非該当 □その他
当センターにおける研究期間	自：1990年04月01日 至：2024年03月31日

Appendix B: Questionnaire on reproductive factors (relevant pages)

Cohort I

PINK FORM – FEMALE -SPECIFIC QUESTIONS

Women, please answer the following questions.

1. How old were you when you first started menstruating? ☐☐ years old

2. Do you still menstruate? 1. Yes | 2. Natural menopause | 3. Artificial menopause

   If you are no longer menstruate, how old were you when menopause began? ☐☐ years old

3. Is/was your menstrual cycle regular? (before menopause, if applicable) 0. No | 1. Yes

   How long is your average menstrual cycle length? ☐☐ Days

4. Have you ever taken female hormone drugs? 0. No | Yes

   If yes, are you currently taking hormones? 1. No | 2. Yes

5. In total, how many pregnancies have you had? ☐☐ times

   At what age was your first pregnancy? ☐☐ years old

6. In total, how many deliveries have you had (including stillbirths) ☐☐ times

   At what age was your first delivery? ☐☐ years old

   Did you breastfeed your children? 0. No | 1. Yes

7. Have you ever been told by a doctor that you have had any of the following diseases?

Check all that apply.	No
Mastopathy, mastitis, mammary gland tumor, uterine fibroids, endometritis, ovarian cyst, others (_____)	

8. Have you undergone any of the following screening tests within the past year?

   Cervical cancer 0. No | 1. Yes Breast cancer 0. No | 1. Yes

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PINK FORM – FEMALE SPECIFIC QUESTIONS

Women, please answer the following questions.

1. How old were you when you first started menstruating? ☐☐ years old

2. Do you still menstruate? 1. Yes | 2. Natural menopause | 3. Artificial menopause

   If you no longer menstruate, how old were you when menopause began? ☐☐ years old

3. How would you describe the regularity of your menstrual cycle? (before menopause if applicable) 1. Irregular | 2. Regular

   How long is your average cycle length? ☐☐ days

4. Have you ever taken hormone therapy for dysmenorrhea, contraception or for menopausal problems? 1. No | 2. Yes

   Are you currently taking hormones? 1. No | 2. Yes

5. In total, how many pregnancies have you had? ☐☐ times

   At what age was your first pregnancy? ☐☐ years old

6. In total, how many deliveries have you had (including stillbirths) ☐☐ times

   At what age was your first delivery? ☐☐ years old

   Did you breastfeed your children? 1. No | 2. Yes

7. Have you ever been told by a doctor that you have had any of the following diseases?

   Check all that apply.

   1. None

   2. mastopathy 3. mastitis
   4. mammary gland tumor 5. Endometriosis 6. fibroids of the uterus
   7. ovarian cyst 8. others (_____)