Menstrual and reproductive factors and type 2 diabetes risk: The Japan Public Health Center-based Prospective Study

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ABSTRACT
Aims/Introduction: Menstrual and reproductive factors, including age at menarche, parity and breast-feeding, have been linked to type 2 diabetes risk. We prospectively investigated the association between these factors and type 2 diabetes risk in a large Japanese cohort.

Materials and Methods: Participants were 37,511 women aged 45–75 years who participated in the baseline (1990–1993), second (1995–1998) and third surveys (2000–2003) of the Japan Public Health Center-based Prospective Study, and who had no history of diabetes at the second survey. Menstrual and reproductive history was ascertained using questionnaires at the baseline and second surveys. Odds ratios of self-reported, physician-diagnosed type 2 diabetes over the 5-year period from the second survey were estimated using logistic regression.

Results: At the third survey, 513 new cases of type 2 diabetes were self-reported. The odds ratios of type 2 diabetes tended to increase with the number of parity, after adjustment for covariates other than body mass index (P for trend = 0.029). The multivariable-adjusted odds ratios of type 2 diabetes for women with three or more births was 1.56 (95% confidence interval 0.96–2.53) compared with those who were nulliparous. The association between parity and type 2 diabetes risk was attenuated after additional adjustment for body mass index (P for trend = 0.12). No factors other than parity were significantly associated with type 2 diabetes risk.

Conclusions: Higher parity might be associated with an increased risk of type 2 diabetes among Japanese women, partly through increasing bodyweight.

INTRODUCTION
Type 2 diabetes is rapidly becoming more widespread across the world1. Data from the International Diabetes Federation show that there were 415 million people with diabetes in 2015, and predicts that this will increase to 642 million by 20401. Notably, diabetes in women is predicted to increase from 199.5 million women affected in 2015 to 313.3 million in 20401. Furthermore, the number of prediabetics is proposed to reach 472 million by 20302. In Japan, the number of diabetics increased from 6.9 to 10 million people from 1997 to 20163. Diabetes and its associated complications reduce quality of life and are a major healthcare burden3, making it of paramount importance to seek and develop strategies to prevent diabetes.

In addition to known risk factors for type 2 diabetes (obesity, physical inactivity, smoking and family history of diabetes), sex hormones have been suggested to influence glucose metabolism. For example, estrogen is known to improve insulin sensitivity and enhance glucose-stimulated insulin secretion4. In fact, some5–6 but not all studies7–10 suggest that early menopause (shorter duration of exposure to estrogen) is correlated with a higher risk of type 2 diabetes. Given that the menstrual cycle is regulated by the balance of estrogen and progesterone, and that
estrogen maintains at a high level during pregnancy and rapidly declines after childbirth, it is possible that menstrual and reproductive factors might also influence type 2 diabetes risk. Meta-analysis studies suggest that a higher risk of type 2 diabetes is linked to early menarche\(^1\) or higher parity\(^2\), whereas a lower risk is linked to breast-feeding\(^3,4\) or hormone-replacement therapy in postmenopausal women\(^5\). Some\(^6-10\) but not all studies\(^11-20\) have also shown an association between long or irregular menstrual cycles and higher risk of type 2 diabetes. Evidence linking menopausal status with diabetes is mixed\(^21\). Furthermore, during pregnancy and after childbirth, not only change of hormone balance, but also lifestyle changes including increased energy intake, change in food choice and physical inactivity might contribute to the development of type 2 diabetes. Japanese women have a much lower body mass index (BMI) – a strong predictor for diabetes – than Western women\(^22\), suggesting that correlations between reproductive factors and type 2 diabetes risk might differ between Japanese and Western populations. In Japan, however, just two studies have reported associations between menopausal status and type 2 diabetes\(^6,8\), whereas no study has investigated the contribution of other menstrual and reproductive factors.

Here, using data from a large-scale population-based cohort study in Japan, we prospectively examined the association of menstrual and reproductive history, including age at menarche and menopause, reproductive life span, menstrual regularity, menstrual cycle length, menopausal status, use of exogenous female hormones, parity, age at first birth and breast-feeding, with type 2 diabetes risk.

**METHODS**

**Study population**

The Japan Public Health Center-based Study was started in 1990 for cohort I and in 1993 for cohort II\(^23\). Residents of 11 Public Health Center areas aged 40–69 years completed the baseline survey. The study sites primarily comprised rural areas throughout Japan. Participants were told of the study objectives, and those who completed the survey questionnaire were considered to have consented to participation. At baseline, 5-year follow up (second survey) and 10-year follow up (third survey), data were collected regarding medical histories, and health-related lifestyle, smoking, drinking and dietary habits using a self-administered questionnaire. This study was approved by the institutional review board of the National Cancer Center of Japan and the ethics committee of the National Center for Global Health and Medicine, Japan.

Of 71,698 female participants, 42,727 completed the questionnaires at the first, second and third surveys (Figure 1). Of these, we excluded 5,216 participants who reported a history of type 2 diabetes \((n = 2,095)\) or severe disease \((n = 3,361)\), including cancer, cerebrovascular disease, myocardial infarction, chronic liver disease and renal disease, at the first or second survey, leaving 37,511 women for analysis. We excluded women with the aforementioned diseases to minimize the potential influence of lifestyle changes and treatment associated with the disease or disease itself on both menstrual and reproductive factors and diabetes risk.

**Reproductive factors**

At the first survey, participants were asked about their menstrual and reproductive history. Questions regarding menstrual and reproductive history included age at menarche, menstrual regularity, menstrual cycle length, use of exogenous female hormones, parity, age at first birth and history of breast-feeding. With respect to female hormone use, as neither oral contraceptives nor hormone replacement therapy were frequently used in Japan at the time the baseline survey was administered\(^24\), participants were simply asked if they had experience using exogenous female hormones without distinction between oral contraceptives and hormone replacement therapy. Menopausal status and age at menopause were also inquired about at the second survey. We asked participant age at menopause by choosing one of six options \((\leq 39, 40–44, 45–49, 50–54, 55–59\) and \(\geq 60\) years). We calculated reproductive life span by subtracting the age at menarche from the age at menopause (age at the start of the follow up for premenopausal women), for which we assigned \(39, 42, 47, 52, 57\) and \(60\) years to the response categories of age at menopause of \(\leq 39, 40–44, 45–49, 50–54, 55–59\) and \(\geq 60\) years, respectively.

**Ascertainment of type 2 diabetes**

For the present analysis, we used the second survey as baseline, because dietary intake, which was treated as an adjustment factor, was assessed by the same questionnaire in cohorts I and II. New diabetes cases diagnosed by a doctor subsequent to the second survey (5-year period) were ascertained by a self-administered questionnaire at the third survey. We validated self-reported physician-diagnosed diabetes by examining participants’ medical records in three districts of the study areas; we found that 94% of self-reported diabetes cases were documented in the corresponding participants’ medical records\(^25\).

**Statistical analysis**

For baseline characteristics, the mean and proportion of women were calculated for each menopausal status. Multiple logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of type 2 diabetes for each of the menstrual and reproductive factors. The first model was adjusted for age and study area, whereas the second model was additionally adjusted for smoking status, alcohol consumption, family history of diabetes mellitus, total physical activity, history of hypertension, total energy intake, coffee consumption, and energy-adjusted daily intake of calcium, magnesium, dietary fiber, vegetable, fruit, rice and meat. Furthermore, when examining the association of type 2 diabetes with age at menopause, reproductive life span and breast-feeding, we also adjusted for reason of menopause (natural or surgical), menopausal status and parity, respectively. The third model was adjusted for all
covariates listed for the second model and BMI. An indicator variable was generated for missing data within each covariate. Trend associations were determined by examining each menstrual and reproductive factor as a continuous variable. A two-sided \( P < 0.05 \) was regarded as statistically significant. All analyses were carried out using Statistical Analysis System (SAS) version 9.3 software (SAS Institute, Cary, NC, USA).

**RESULTS**

Across the 5-year period, 513 participants received new diagnoses of diabetes. Table 1 shows the characteristics of study participants stratified by menopausal status. At baseline, 22% of participants were premenopausal. The mean age and BMI was 56.9 years and 23.4 kg/m\(^2\), respectively.

Table 2 summarizes the ORs and 95% CIs of type 2 diabetes for the examined menstrual and reproductive factors. Higher parity was associated with an increased risk of type 2 diabetes in a model adjusted for covariates other than BMI. The multivariable-adjusted ORs of type 2 diabetes were 1.00 (reference), 1.23 (95% CI 0.68–2.21), 1.37 (95% CI 0.83–2.24) and 1.56 (95% CI 0.96–2.53) for women with nulliparous, one, two and three or more births, respectively (\( P \) for trend = 0.029). The association was somewhat attenuated after additional adjustment for BMI (\( P \) for trend = 0.12); the corresponding ORs were 1.00 (reference), 1.18 (95% CI 0.65–2.13), 1.30 (95% CI 0.79–2.14) and 1.40 (95% CI 0.86–2.28). Women who had breast-fed had lower, albeit not statistically significant, odds of type 2 diabetes than women who had never breast-fed (multivariable-adjusted [including parity] OR 0.83, 95% CI 0.63–1.09). Other menstrual and reproductive factors, including age at menarche and menopause, reproductive life span, menopausal status, menstrual cycle, use of female hormones, age at first birth, and breast-feeding, were not significantly associated with type 2 diabetes risk.

**DISCUSSION**

We found that higher parity was associated with an increased risk of type 2 diabetes, and this association was somewhat attenuated after additional adjustment for BMI. Women with breast-feeding experience had a lower type 2 diabetes risk. To our knowledge, this is among a few studies to inclusively examine the association between menstrual and reproductive factors and type 2 diabetes risk in Asia, and is the first such study in Japan.
A meta-analysis of seven cohort studies\(^\text{12}\) showed that higher parity was significantly correlated with a higher risk of type 2 diabetes; the combined relative risk for type 2 diabetes of the highest versus lowest category of parity was 1.42 (95% CI 1.17–1.72). The higher combined relative risk was slightly lower in models that did adjust for BMI compared with those that did not; the combined relative risk per one live birth was 1.04 (95% CI 1.01–1.09) and 1.09 (95% CI 1.02–1.16) with and without adjustment for BMI, respectively. Similar to that meta-analysis, we also found that adjustment for BMI attenuated the association between parity and type 2 diabetes risk. These findings suggest that a higher risk of type 2 diabetes due to parity might be partly explained by weight gain after childbearing. In the present study population, BMI tended to increase with the number of parity; the age-adjusted mean BMI was 22.8, 23.0, 23.1 and 23.8 kg/m\(^2\) among women who were nulliparous, and those who had one, two and three or more births, respectively. Weight control after childbearing might be important for preventing type 2 diabetes among parous women. Some studies have suggested that mechanisms other than weight gain might underlie the association between parity and type 2 diabetes. High levels of hormones secreted during pregnancy, including estrogen, progesterone, chorionic somatomammotropin and corticosteroids, interfere with the role of insulin in carbohydrate uptake and utilization. This can result in peripheral insulin resistance such that increased levels of insulin are required to sustain glucose tolerance\(^\text{26}\).

We found that women who had breast-feeding experience had reduced odds of developing type 2 diabetes compared with

### Table 1 | Characteristics of study participants at baseline

|                          | All women | Premenopausal women | Postmenopausal women |
|--------------------------|-----------|---------------------|----------------------|
| n                        | 37,511    | 8,401               | 26,540               |
| Age (years)              | 56.9 ± 7.9| 47.7 ± 2.6          | 59.4 ± 6.7           |
| Body mass index (kg/m\(^2\)) | 23.4 ± 3.1| 23.2 ± 3.0          | 23.5 ± 3.1           |
| Total physical activity (MET-h/day) | 32.9 ± 5.7| 32.8 ± 5.7          | 32.9 ± 5.7           |
| Current smoker (%)       | 4.7       | 6.5                 | 4.2                  |
| Current drinker, ≥1 day/week (%) | 12.6     | 18.9                | 11.0                 |
| Family history of diabetes (%) | 8.7       | 10.7                | 8.3                  |
| History of hypertension (%) | 18.5     | 63                  | 21.8                 |
| Coffee consumption, ≥1 cup/day (%) | 37.0   | 52.4                | 32.7                 |
| Dietary intake (g/day)   |           |                     |                      |
| Total energy intake (kcal) | 1,931 ± 779| 1,976 ± 768        | 1,936 ± 766          |
| Magnesium\(^\dagger\) (mg) | 269 ± 51       | 257 ± 46            | 273 ± 51             |
| Calcium\(^\dagger\) (mg) | 542 ± 214   | 514 ± 202           | 550 ± 212            |
| Dietary fiber\(^\dagger\) (g) | 13.1 ± 4.4    | 12.3 ± 4.0          | 13.4 ± 4.4           |
| Vegetable\(^\dagger\) (g) | 227 ± 135    | 206 ± 116           | 234 ± 137            |
| Fruit\(^\dagger\) (g) | 241 ± 182   | 216 ± 154           | 249 ± 181            |
| Rice\(^\dagger\) (g) | 342 ± 136   | 339 ± 131           | 342 ± 136            |
| Meat\(^\dagger\) (g) | 55 ± 41     | 58 ± 36             | 54 ± 39              |
| Age at menarche (years)  | 14.7 ± 1.9  | 13.6 ± 1.4          | 14.9 ± 1.9           |
| Age at menopause (%)     |           |                     |                      |
| <45 years                | –         | –                   | 13.2                 |
| 45–49 years              | –         | –                   | 33.8                 |
| 50–54 years              | –         | –                   | 48.0                 |
| ≥55 years                | –         | –                   | 50.0                 |
| Reproductive life span\(^\ddagger\) (years) | 34.6 ± 3.8    | 34.1 ± 2.6          | 34.8 ± 4.1           |
| Menstrual regularity, regular (%) | 80.4   | 85.7                | 78.6                 |
| Menstrual cycle length, if regular cycle (days) | 28.1 ± 2.2    | 27.9 ± 2.3          | 28.2 ± 2.1           |
| Use of female hormones, current user (%) | 1.2       | 1.1                 | 1.2                  |
| Parity (%)               |           |                     |                      |
| Nulliparous              | 5.5       | 5.5                 | 5.4                  |
| 1 time                   | 6.9       | 6.6                 | 7.1                  |
| 2 times                  | 36.2      | 43.2                | 34.9                 |
| ≥3 times                 | 51.4      | 44.7                | 52.5                 |
| Age at first birth among parous women (years) | 24.9 ± 3.4    | 25.1 ± 3.4          | 24.8 ± 3.4           |
| Breastfeeding among parous women, yes (%) | 87.7     | 85.8                | 88.2                 |

Data are presented as mean ± standard deviation. \(^\dagger\) Energy-adjusted intake. \(^\ddagger\) The interval between the age at menarche and menopause (age at the start of the follow up for premenopausal women). MET, metabolic equivalent; SD, standard deviation.
| Menstrual cycle length (if regular cycle) (day) | Odds ratios and 95% confidence intervals for type 2 diabetes according to menstrual and reproductive factors |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------|
| Age at menarche (years)                       | 1.00 (Reference)                                                                                   |
| 14                                            | 0.97 (0.75–1.25)                                                                                    |
| 15                                            | 0.87 (0.66–1.15)                                                                                    |
| ≥16                                           | 0.93 (0.71–1.23)                                                                                    |
| Menopausal status                             |                                                                                                   |
| Premenopausal                                  | 1.00 (Reference)                                                                                   |
| Postmenopausal                                 | 1.16 (0.86–1.57)                                                                                    |
| Age at menopause (years)                      |                                                                                                   |
| ≤44                                           | 1.44 (1.07–1.93)                                                                                    |
| 45–49                                         | 1.12 (0.89–1.42)                                                                                    |
| 50–54                                         | 1.00 (Reference)                                                                                    |
| ≥55                                           | 1.14 (0.71–1.82)                                                                                    |
| Reproductive life span (years)                |                                                                                                   |
| ≤28                                           | 1.00 (Reference)                                                                                    |
| 29–31                                         | 0.66 (0.45–0.97)                                                                                    |
| 32–34                                         | 0.75 (0.55–1.03)                                                                                    |
| 35–37                                         | 0.70 (0.51–0.96)                                                                                    |
| ≥38                                           | 0.73 (0.53–1.01)                                                                                    |
| Menstrual regularity                          |                                                                                                   |
| Irregular                                     | 1.03 (0.81–1.29)                                                                                    |
| Regular                                       | 1.00 (Reference)                                                                                    |
| Menstrual cycle length (if regular cycle) (day)|                                                                                                   |
| ≤25                                           | 0.91 (0.63–1.33)                                                                                    |
| 26–27                                         | 0.84 (0.52–1.38)                                                                                    |
| 28–29                                         | 1.00 (Reference)                                                                                    |
| ≥30                                           | 1.14 (0.89–1.46)                                                                                    |
| Use of female hormones                        |                                                                                                   |
| Never                                         | 1.00 (Reference)                                                                                    |
| Past                                          | 0.92 (0.67–1.25)                                                                                    |
| Current                                       | 1.43 (0.70–2.90)                                                                                    |
| Parity (times)                                |                                                                                                   |
| Nulliparous                                   | 1.00 (Reference)                                                                                    |
| 1                                             | 1.28 (0.71–2.31)                                                                                    |
| 2                                             | 1.37 (0.84–2.24)                                                                                    |
| ≥3                                            | 1.56 (0.96–2.52)                                                                                    |
| Age at first birth among parous women (years) |                                                                                                   |
| ≤22                                           | 1.00 (Reference)                                                                                    |
| 23–25                                         | 0.92 (0.72–1.16)                                                                                    |
| 26–29                                         | 1.01 (0.78–1.30)                                                                                    |
| ≥30                                           | 0.83 (0.56–1.23)                                                                                    |
| Breast-feeding among parous women             |                                                                                                   |
| No                                            | 1.00 (Reference)                                                                                    |
| Yes                                           | 0.81 (0.62–1.06)                                                                                    |

*Adjusted for age (years) and study area (11 areas). †Adjusted for age (years), study area (11 areas), smoking status (never, past, current with a consumption of <20 or ≥30 cigarettes/day), alcohol consumption (non-drinker, occasional drinker or drinker with a consumption of <150 or ≥150 g ethanol/week), family history of diabetes mellitus (yes or no), total physical activity (quartile), metabolic equivalent-h/day), history of hypertension (yes or no), total energy intake (kcal/day, quartile), coffee consumption (almost never, <1, or ≥2 cups/day), energy-adjusted daily intake of foods or nutrients (calcium, mg; magnesium, mg; dietary fiber, g; vegetable, g; fruit, g; rice, g; meat, g; quartile). For the association between age at menopause and type 2 diabetes, reason of menopause (natural or surgical) was adjusted for. For the association between reproductive life span and type 2 diabetes, menopausal status (premenopause, natural menopause or surgical menopause) was adjusted for. For the association between breast-feeding and type 2 diabetes, parity was adjusted for. ‡Additionally adjusted for body mass index (<21, 21–22.9, 23–24.9, 25–26.9 or ≥27 kg/m²). §The interval between the age at menarche and menopause (age at the start of the follow up for premenopausal women). CI, confidence interval; OR, odds ratio.
those who did not. A meta-analysis of six cohort studies and five cross-sectional or case-controlled studies likewise showed a correlation between breast-feeding and decreased risk of type 2 diabetes, with a pooled OR of 0.65 (95% CI 0.49–0.86) among breast-feeding women compared with non-breast-feeding women. Another meta-analysis study of six cohort studies showed a reduced risk of type 2 diabetes with increasing lifetime breast-feeding duration. These findings suggest a potential correlation between breast-feeding and reduced risk of type 2 diabetes among parous women.

A meta-analysis study showed that early menarche was correlated with a higher risk of type 2 diabetes, whereas hormone-replacement therapy in postmenopausal women was linked to a reduced risk. Although the evidence is mixed, early menopause, long or irregular menstrual cycle and postmenopausal status have been linked to a higher risk of type 2 diabetes. Here, however, we did not find any associations between these factors and type 2 diabetes risk. Although the reason for this discrepancy is unclear, it might be partly explained by differences in the association between these factors and BMI between the study populations. For example, some studies that showed an inverse correlation between age at menarche and type 2 diabetes also showed that adjustment for BMI attenuated this correlation, because earlier menarche was linked to increased BMI. In contrast, we did not find a correlation between age at menarche and BMI; the age-adjusted mean BMI was 23.5, 23.4, 23.4 and 23.5 kg/m2 for age at menarche categories of <14, 14, 15 and ≥16 years, respectively.

The present study had many strengths, such as its large sample size, population-based prospective design and the accounting for or grouping according to possible confounding variables. However, there were some limitations. First, type 2 diabetes diagnoses were collected by self-report. However, we validated these reports and found fairly good agreement between self-reported accounts and participants’ medical records. Second, we did not include women who reported a history of diabetes at baseline because of no information about the timing of diabetes diagnosis in relation to exposure event (for instance, before or after childbirth). The observed associations in the present study thus reflect the risk of type 2 diabetes associated with menstrual and reproductive factors during middle-to-late adulthood, but might not be applied to that during early adulthood. Third, we did not have data on breast-feeding duration. Fourth, exposure assessment by self-report might be subject to recall bias (particularly among older women). Finally, we cannot rule out potential unmeasured and residual confounding effects, including by socioeconomic status.

In conclusion, we showed that an increased risk of type 2 diabetes was associated with higher parity among Japanese women, which could be partly attributable to increased body-weight after childbirth. Other menstrual and reproductive factors, including age at menarche and menopause, reproductive life span, menopausal status, menstrual cycle, use of female hormones, age at first birth, and breast-feeding, were not appreciably associated with type 2 diabetes risk. As evidence on this issue in Asia is limited, further studies among Asian populations are required.

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DISCLOSURE
The authors declare no conflict of interest.

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