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Abstract. Early menarche is known to be associated with diabetes, however this association remains controversial. Our study aimed to investigate the possible association between age at menarche and diabetes prevalence in post-menopausal Korean women. This study included 3,254 post-menopausal Korean women aged 50-85 years from the Korea National Health and Nutrition Examination Survey IV (KNHANES 2007–2009). Logistic regression analyses were used to estimate odds ratios (ORs) for diabetes prevalence. Levels of biochemical markers were compared according to groups by age at menarche. Women in the earlier menarche age group (10-12 years) showed higher levels of fasting blood glucose (FBG) and scores of homeostatic model assessment in the insulin resistance (HOMA-IR) index than other groups (p<0.05). After adjusting for potential confounding factors, early age at menarche was significantly associated with a higher prevalence of diabetes (OR 1.86, 95% confidence intervals [CI] 1.07–3.23). The observed association remained significant despite additional adjustment for body mass index and waist circumference (OR 1.82, 95% CI 1.03–3.23) and despite further adjustments for FBG levels and HOMA-IR index (OR 2.25, 95% CI 1.11–4.55). Our findings strengthen the hypothesis that younger age at menarche is associated with increased diabetes prevalence in the Korean population.

Key words: Menarche, Diabetes, Body mass index, Waist circumference, Fasting blood glucose

POST-MENOPAUSAL women are highly exposed to multiple health problems and risk of diabetes is higher in postmenopausal women than in their pre-menopausal counterparts [1]. Diabetes decrease health-related quality of life because of diabetic complications, and increase burden of disease [2]. Considering the fact that diabetes–caused death rate per 100,000 is 37.5 in women aged 50-69 years and 186.9 in women aged 70-80 years, whereas 2.7 in women aged 15-49 years, prevention and treatment for diabetes are an important health issue for post-menopausal women [3].

Age at menarche is defined as the age at the onset of menstruation in adolescents and is frequently used as a marker of puberty timing. Previous studies have suggested the possibility that age at menarche affects women’s health problems such as high glucose levels, insulin resistance (IR) and adiposity [4-6], which conditions are strongly related with diabetes. Association between age at menarche and diabetes prevalence in women remains controversial. Several studies proved that early menarche was associated with higher prevalence of diabetes [7-9]. However, other studies found no association [10, 11]. Since the discrepancy may be attributed to different characteristics of subjects including age, menopausal status and types of diabetes, study on subjects with homogenous characteristics is needed.

Similar to western people [12], the age at menarche has been reported to decrease in the Korean women [13, 14]. It is concurrent with a trend in elevated diabetes prevalence, and raises the question whether the age at menarche is associated with diabetes in the Korean women. Recently, two studies reported that early men-
arche increases the risk of diabetes in young and middle-aged Korean women [9, 15]. However, there are some limitations regarding size of population and their heterogeneous characteristics such as menopause status and age. For example, in case of younger subjects, there is possibility of being type1 diabetes patients or pre-menopausal women who have quite different metabolic process compared with that of type 2 diabetes patients or post-menopausal women [16, 17]. To overcome these limitations, this study was designed to investigate whether age at menarche is associated with diabetes prevalence in post-menopausal Korean women aged 50 to 85 years using a large representative dataset from the Korea National Health and Nutrition Examination Survey IV (KNHANES IV).

**Materials and Methods**

**Study population**

The target population for this study was obtained from the KNHANES IV (2007–2009). The KNHANES is a national representative survey with a cross-sectional design used to assess the health and nutritional status of Koreans since 1998. The survey was conducted by the Korea Centers for Disease Control and Prevention (KCDC). The KNHANES recruits new samples of approximately 10,000 individuals annually using a stratified multi-stage probability cluster sampling method. The KNHANES includes health interviews, health examinations and nutrition survey. Details about the KNHANES have been described previously [18]. The response rate of the survey was 71.2% in 2007, 77.8% in 2008, and 82.8% in 2009.

Among 24,871 KNHANES participants in 2007–2009, we included only post-menopausal women aged 50 to 85 years according to previous studies (Fig. 1) [17, 19, 20]. Women aged less than 50 years were excluded to minimize the women with artificial menopause [17], and hereditary diabetes [19]. In addition, women who aged 50 years or older were considered as post-menopausal since they located on more than average age of menopause among Korean women (mean age at menopause: 49.4 ± 5.1 years) [17]. Then, we exclude pre-menopausal women based on data of menstruation which was obtained by self-reported questionnaire. Subjects answered following questions: “Are you on a menstruation period currently?” or “When was your age at menopause?” Women who had reported their age at menopause had menopause or hysterectomy were defined as post-menopausal. Women aged over 85 years were excluded to avoid information bias regarding the response to the age at menarche question [20]. Women with onset of age at menarche under 10 years and over 18 years were excluded. We also excluded respondents with missing responses for important variables such as menstruation, age at menarche, insulin levels, fasting blood glucose (FBG) levels, and a diabetes diagnosis. In addition, women taking medication for diabetes, hypertension or dyslipidemia on the day of the examination were excluded to eliminate treatment effects that could affect our results [21]. Pregnant or lactating women were also excluded because of their distinct hormonal changes. Our final sample for statistical analysis comprised 3,254 women.

The KNHANES was approved by the Institutional Review Board of the KCDC. The database is available to the public at the website of KNHANES (http://knhanes.cdc.go.kr) [18]. All study participants provided written informed consent.

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**Fig. 1** Flow chart of study population
**General characteristics of the subjects**

We obtained socio-demographic and anthropometric data from the KNHANES to assess the general characteristics of the women included in this study. Socio-demographic characteristics included household income and education level. Household income was divided into quartiles and reported in the South Korean currency “won” as follows: lowest (≤1 million won), lower-middle (1–2 million won), upper-middle (2–3 million won), and highest (>3 million won). Education level was categorized into four groups: ≤ elementary school, ≤ middle school, ≤ high school, or ≥ university. Anthropometric measurements were conducted by a trained expert. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as weight (kg)/height squared (m²), and women were classified into one of three groups: underweight (<18.5 kg/m²), normal weight (18.5–25 kg/m²), or obese (≥25 kg/m²).

Waist circumference (WC) was measured at the area between the rib cage and the iliac crest to the nearest of 0.1 cm and categorized as two groups: ≥80 cm and <80 cm. Physical activity was also divided into two groups: exercise or no exercise. Exercise was defined as participation in any of the following: intense physical activity for 20 min for at least 3 days/week, moderate physical activity for 30 minutes for at least 5 days/week, or walking for 30 min/day for at least 5 days/week. Current smokers were defined as person who smoked more than 5 packs in one’s lifetime and who smoke cigarettes currently. Women who drank alcohol at least once a month in the last year were considered current alcohol consumers. Women who were taking oral contraception or receiving hormonal treatment were considered as taking hormonal medication. Respondents were considered to have hypertension, dyslipidemia if they were diagnosed as such by a physician, and considered to have cardiac disease if they were diagnosed with myocardial infarction or angina pectoris by a physician.

**Assessment of age at menarche**

Information on the age at menarche was obtained by the question “When did you have your first menstrual period?” Age at menarche was defined as the age at the first menstrual period. Based on a previous study [22], we categorized the age at menarche as three groups: early age at menarche (EMA, 10–12 years), normal age at menarche (NMA, 13–15 years), and late age at menarche (LMA, 16–18 years). NMA was based on the median age at menarche seen in the study sample (14 years).

**Definition of and diagnostic criteria for diabetes**

According to previous study [23], diabetes was defined using self-reported questionnaire; “Have you been diagnosed with diabetes by a physician?” Both, type 1 and type 2 diabetes were considered as diabetes. Subjects who answered, “I have been diagnosed with diabetes” were considered to have diabetes, and those reporting “I have not been diagnosed with diabetes” or “I have never been diagnosed with diabetes” were considered to not have diabetes. Women who responded with “I do not know” were considered to have missing values [24].

**Biochemical measurements**

Blood samples were collected from the antecubital vein after fasting for 10–12 hours to assess the serum levels of biochemical markers. Systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg) were measured by a mercury sphygmomanometer (Baumanometer; NY, USA) on the right arm. Serum levels of triglycerides (TG; mg/dL), total cholesterol (TC; mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), fasting blood glucose (FBG; mg/dL), aspartate aminotransferase (AST; IU/L), and alanine aminotransferase (ALT; IU/L) were measured with an automatic analyzer (Hitachi 7600, Hitachi; Tokyo, Japan). In women with TG levels ≤400 mg/dL, LDL cholesterol was calculated using the following equation: LDL cholesterol (mg/dL) = total cholesterol (mg/dL) – HDL cholesterol (mg/dL) – (TG (mg/dL)/5). Serum insulin levels (μIU/mL) were measured by an immunoradiometric assay using a 1470 Wizard Gamma Counter (PerkinElmer; Turku, Finland). Hemoglobin A1c (HbA1c; %) levels were measured using high-performance liquid chromatography-723G7 (Tosho; Tokyo, Japan). The homeostatic model assessment (HOMA) was used to evaluate pancreatic IR [25]. HOMA-IR was assessed using the following equation: [fasting insulin (μIU/mL) × FBG (mg/dL)]/405.

**Statistical analysis**

Statistical analyses were performed using SPSS version 21.0 (IBM; Chicago, USA). Continuous variables are described as mean ± standard error, and categori-
BMI and WC, and model 4 was additionally adjusted for FBG levels and HOMA-IR index. A p-value <0.05 was considered statistically significant.

### Results

#### General characteristics by age at menarche

The general characteristics of the respondents are represented in Table 1. The mean age of the women participating in this study was 64.1 ± 0.2 years and mean age at menarche was 15.67 ± 0.03 years. Age showed a tendency for an increase with the age at menarche (p <0.001). Women in the EMA group were younger and more educated than other groups (p <0.001). Also, prevalence of hypertension, dyslipidemia and cardiac disease, and diabetes tended to be higher in the EMA group than NMA group.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the subjects according to groups by age at menarche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups by age at menarche</td>
<td>p-value*</td>
</tr>
<tr>
<td></td>
<td>Total (n=3,254)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.1 ± 0.2</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>15.67 ± 0.03</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 ± 0.1</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>83.4 ± 0.2</td>
</tr>
<tr>
<td>Income %, (n)</td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>39.0 (1228)</td>
</tr>
<tr>
<td>Lower middle</td>
<td>26.6 (837)</td>
</tr>
<tr>
<td>Upper middle</td>
<td>17.7 (557)</td>
</tr>
<tr>
<td>Highest</td>
<td>16.7 (525)</td>
</tr>
<tr>
<td>Education %, (n)</td>
<td></td>
</tr>
<tr>
<td>≤ Elementary school</td>
<td>68.9 (2236)</td>
</tr>
<tr>
<td>≤ Middle school</td>
<td>13.7 (443)</td>
</tr>
<tr>
<td>≤ High school</td>
<td>12.9 (418)</td>
</tr>
<tr>
<td>≥ University</td>
<td>4.6 (148)</td>
</tr>
<tr>
<td>Disease diagnosis</td>
<td></td>
</tr>
<tr>
<td>Hypertension %, (n)</td>
<td>38.5 (1254)</td>
</tr>
<tr>
<td>Dyslipidemia %, (n)</td>
<td>15.1 (490)</td>
</tr>
<tr>
<td>Cardiac disease %, (n)**</td>
<td>3.8 (124)</td>
</tr>
<tr>
<td>Diabetes %, (n)</td>
<td>13.4 (437)</td>
</tr>
<tr>
<td>Physical activity %, (n)</td>
<td>55.2 (1782)</td>
</tr>
<tr>
<td>Drinker %, (n)</td>
<td>23.0 (746)</td>
</tr>
<tr>
<td>Smoker %, (n)</td>
<td>4.3 (138)</td>
</tr>
<tr>
<td>Use of hormonal medication %, (n)</td>
<td>32.6 (1059)</td>
</tr>
</tbody>
</table>

Age, age at menarche, body mass index (BMI) and waist circumference (WC) are presented as mean ± standard error (SE). Income, education, diagnosis of hypertension, dyslipidemia cardiac disease and diabetes, physical activity, drinker, smoker and use of hormonal medication are shown as percentages of total subjects. *Statistical significance determined by one-way ANOVA for continuous variables and Chi square tests for categorical variables (p <0.05). **Cardiac disease includes myocardial infarction and angina pectoris. Values with the same letters indicate that no significant differences were found between the groups. BMI, body mass index; EMA, early menarche age; NMA, normal menarche age; LMA, late menarche age; WC, waist circumference.
**Biochemical marker levels by age at menarche groups**

The comparison of the levels of biochemical markers among age at menarche groups is shown in Table 2. Women in the EMA group had higher levels of SBP, TG, FBG, and HbA1c, and lower HDL-C than NMA group before adjustment (*p* <0.05). However, the statistical significances changed after the adjustment for possible confounders. After adjustment, we found a significant inverse association between age at menarche and FBG levels and the HOMA-IR index (*p* <0.05).

**Odds ratios (ORs) for diabetes by age at menarche**

Based on difference of general characteristics and levels of biochemical markers, we analyzed odds ratios (ORs) for diabetes according to age at menarche. The ORs for diabetes by 3 groups (EMA, NMA and LMA) are shown in Table 3. Before adjustment, the EMA group showed significantly high OR for diabetes than NMA group (OR 1.80, 95% CI 1.08–2.99) (data not shown). After adjustment, the EMA group still showed significantly high OR for diabetes than NMA group in all models. The association was stron-
gest after additional adjustment for FBG levels and the HOMA-IR index (Model 4: OR 2.25, 95% CI 1.11–4.55). However, the LMA group showed no significant OR for diabetes compared to NMA group in all models (Model 1: OR 0.88, 95% CI 0.71–1.11; Model 2: OR 0.91, 95% CI 0.72–1.14; Model 3: OR 0.92, 95% CI 0.73–1.16, Model 4: OR 1.01, 95% CI 0.76–1.34).

Discussion

Since pubertal development at early life may be an important determinant of onset of various diseases in adulthood [26], a possible association of the timing of pubertal development and diabetes is an emerging concern. Several large prospective cohort studies have demonstrated that early menarche is associated with increased risk of diabetes in adulthood [27, 28]. Very recently, cross-sectional studies on Korean women have reported the association between early menarche and diabetes prevalence [9, 15], implying that early menarche may exacerbate glucose metabolism and cause diabetes. However, other studies reported inconsistent results that age at menarche is not associated with diabetes in African-American and China women [10, 11]. It is difficult to draw clear conclusions yet, but these differences may be attributed to race and characteristics of subjects.

In the present study, consistent with previous results [8, 9, 29], age at menarche was inversely associated with diabetes prevalence even in post-menopausal Korean women. The subjects with age at menarche younger than 13 years showed high ORs for diabetes. The exact mechanism regarding the association between the age at menarche and diabetes could not be explained, but several possible pathways reflecting a linkage between puberty onset and diabetes could be implicated. First, earlier menarche may induce longer exposure of estrogen [30]. Estrogen plays an important role in the development of type 2 diabetes [31] through inhibiting the production of insulin-like growth factor (IGF-1) which promotes pancreatic growth and beta-cell mass [32]. Therefore, earlier menarche may cause diabetes by impairing pancreatic function mediating estrogen. Second, genetic factors may involve the association between age at menarche and diabetes. Genetic factors are known to influence the age at menarche in 57–82% of women [33]. Korean genome-wide association studies suggested that the age at menarche interacts with a single nucleotide polymorphism in the IGF-2 receptor gene [34], which contributes to the development of diabetes [35]. During the preparation of this manuscript, two studies have just reported in Korea which found inverse association between early age at menarche and diabetes. One study [9] was conducted in young and middle-aged Korean women, which may include pre-menopausal mostly. The other study [15] found inverse association of earlier age at menarche and diabetes in middle-aged Korean women belonging to the middle class. In line with these studies, our study added supporting evidence on association between early menarche age and diabetes in middle and older-aged Korean women.

Several studies conducted in western population have suggested that adiposity may mediate the association between age at menarche and diabetes [27, 36]. Lakshman et al. [27] and Elks et al. [36] found that the significance of inverse association between age at menarche and diabetes disappeared after adjustment for BMI. However, in our study, the association between earlier age at menarche and diabetes remained significant additionally adjusting for adiposity such as BMI and WC. This indicates that adiposity may not be a mediating factor for association between early age at menarche and diabetes in post-menopausal Korean women, who have relatively lower BMI than westerners [37]. It is consistent with a report of Lim et al. [9], which showed statistically significant association between early age at menarche and type 2 diabetes after further adjustment for BMI. In contrast, Baek et al. [15] reported that significance on association between early age at menarche and diabetes disappeared after additionally adjusting for adiposity. However, they did not suggest adiposity as a mediating factor due to small number of diabetes patients. To identify the association between age at menarche and diabetes is independent of adiposity, more detailed study using subject stratified by adiposity should be conducted.

This study had several limitations. First, we relied on retrospective reporting of the age at menarche, which raises the possibility of information bias. However, a prospective study demonstrated that the age at menarche recalled in adulthood and the actual age at menarche are highly correlated [38]. To minimize this bias, we excluded very old subjects over the age of 85. Second, no causal relationship between the age at menarche and diabetes could be established in our study, as the analysis of our data was conducted at one specific point in time. However, we can rule out a reverse causal
relationship between the age at menarche and diabetes, because the onset of menarche might be occurred before diagnosis of diabetes. Third, we couldn’t distinguish the types of diabetes because detailed information on this variable was not available in KNHANES. To minimize the inclusion of women with hereditary diabetes, we limited our study to women aged 50 and more than 50 years [19]. Finally, we could not consider other variables that are known as important risk factors for diabetes later in life (e.g., childhood anthropometric measurements) [39]. However, since obesity has a tendency to persist from childhood into adulthood [40], it is plausible to use BMI in adulthood instead of BMI in childhood. Despite of these limitations, our study has meaningful strengths. First, we used a large and representative data granting strong statistical power. Second, our subjects have homogeneous characteristics such as Korean, middle and old aged women, and post-menopausal status which may minimize the effect of possible confounding factors, such as race, age and menopause status. Third, we considered various confounding factors for adjustments. Finally, the anthropometric data were acquired by measurement on the check-up day rather than self-reporting to reduce possible bias by recall.

In conclusion, an earlier age at menarche is associated with high risk of diabetes in post-menopausal Korean women. This implies that the time of entry into puberty for women may be an important factor for the development of diabetes in adulthood. Our results suggest that assessing age at menarche may help early identification of diabetes and related morbidities, and contribute to improve health status of post-menopausal women. Further research should focus on the underlying genetic factors linking the age at menarche and diabetes. In addition, longitudinal studies considering non-genetic environmental determinants and childhood factors are required to clearly confirm the association between age at menarche and diabetes in post-menopausal women.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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