Body mass index at age 18–20 and later risk of spontaneous abortion in the Health Examinees Study (HEXA)

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Abstract

Background: Spontaneous abortion (SA) affects 11.2% of recognized pregnancies in Korea. Many studies have focused on the increased risk of SA in obese populations, but there are few studies that have focused on underweight (Body mass index (BMI) <18.5 kg/m²) women, especially in relation to pre-pregnancy BMI. The aim of this study was to examine the role of pre-pregnancy BMI at age 18–20 in later SA.

Methods: Among the women who were ever pregnant in the Health Examinees Study (HEXA), which was one of the cohorts studied in the KoGES (Korean Genome and Epidemiology Study) from 2004 to 2012 (N = 80,447), the likelihood of SA based on pre-pregnancy BMI, classified by the criteria for Asians (Underweight: <18.5 kg/m²; Normal range: 18.5–22.9 kg/m²; Overweight at risk: 23–24.9 kg/m²; Obese I: 25–29.9 kg/m²; Obese II: ≥30 kg/m²), was presented as odds ratios (ORs) and 95% confidence intervals (95% CIs) using logistic regression models.

Results: Being underweight or obese relative to the normal weight range was associated with a higher likelihood of SA (OR = 1.10 [95% CI = 1.05–1.15] in underweight women and OR = 1.06 [95% CI = 0.96–1.16] in obese women), and this effect was much greater in women who experienced recurrent SAs (for three or more SAs: OR = 1.29 [95% CI 1.14–1.46] in underweight women and OR = 1.39 [95% CI 1.09–1.78] in obese women). Obesity was associated with an increased likelihood of SA at a younger age (≤25 years), whereas underweight was associated with an increased OR of SA at an older age (≥26 years).

Discussion: As this study was conducted with baseline data of original cohort which focused on other chronic diseases, recall for previous pregnancy-related information might be less accurate. However, this study shows strength in its large size and prospective potential.

Conclusions: Pre-pregnancy BMI at ages 18–20 years revealed a U-shaped association with SA, and underweight and obese women showed increased likelihood for SA during different age periods.

Background

Spontaneous abortion (SA), or miscarriage, is defined as a clinically observed pregnancy that is lost or that ends before the 20th week of gestation [1]. According to the Korean national survey on Fertility, Family Health & Welfare 2012, SA affects 11.2% of recognized pregnancies, which can be viewed as a rather frequent medical phenomenon [2].

Maternal overweight and obesity are related to increased risk of stillbirth, neonatal and infant death, large for gestational age (LGA), fetal malformations, maternal diabetes, pregnancy-induced hypertension, pre-eclampsia and a high frequency of Caesarean section [3–6]. In obese women, folliculogenesis, ovulation and conception are more likely to be impaired, and pregnancy complications frequently occur [7].

In accordance with the known mechanism linking obesity and SA, there are multiple epidemiologic studies reporting the association between these two factors [8, 9]. Many studies focusing on obese or overweight mothers and their adverse outcomes related to pregnancy have...
been published [4–6], but studies on underweight mothers are rare [10]. Likewise, an association between prepregnancy body mass index (BMI) and adverse pregnancy outcomes has been assessed in several studies [11, 12], but similar studies are uncommon in Asian populations.

It is known that bodyweight in early life is associated with morbidity in adult life [13]. In the Nurses’ Health Study (NHS), women with a BMI greater than 25 kg/m² at age 18 had an increased risk of premature death, and this association was only partially explained by adult obesity [14]. Likewise, there are studies suggesting a crucial effect of early life BMI on later parity [15, 16]. Another study from NHS with 17 years of follow-up also revealed that BMI at age 18 was associated with anovulatory infertility [17]. As BMI in the early years of life seems to affect maternal health, in this study, we aim to evaluate the association between underweight, as well as obesity, at age 18–20 and the risk of SA in the Korean population.

Methods

Subject selection

The eligible population was selected from the Health Examinees Study (HEXA). The HEXA comprises a large-scale genomic community-based prospective cohort of 170,094 participants and biological samples between 2004 and 2012. The HEXA was specifically conducted to evaluate epidemiologic characteristics and genomic risk factors focusing on major chronic diseases, including cancer, in the Korean population. It is a component of the Korean Genome and Epidemiology Study (KoGES). Participating centers were chosen after strict evaluation of the selection criteria and community representativeness of participating hospitals. Recruited subjects were drawn from the community’s adult population, ages 40 to 69 years. Information on general lifestyle, including smoking and drinking habits, physical activity, past medical history, family medical history, drug use (including health supplements), health check-ups, psychological factors, diet and reproductive factors, was obtained by trained interviewers with a structured questionnaire. This questionnaire was developed from an extensive literature review of other questionnaires, including the Korea National Health and Nutrition Examination Survey (KNHANES) [18], which is a representative epidemiologic study of Korea funded by the Korean Center for Disease Control (KCDC). The questionnaire was validated using back translation with English, and a pilot study was conducted to evaluate its efficacy and feasibility [19]. Furthermore, anthropometric measures were performed by trained interviewers, and laboratory tests for blood and urine were conducted by central laboratory. More details about the HEXA can be found elsewhere [19].

Of the total participants, 111,600 participants were women. Among them, 8,605 women were excluded because they had an age other than 40–69 years, no experience of pregnancy, or no information on their parity. Additionally, we excluded the 20,729 women who had missing information on weight or height at ages 18–20 years. A total of 1,244 women with a first pregnancy before age 18 or 20 or with unknown age of first pregnancy and 316 women with missing data on spontaneous abortion were also excluded. Finally, a total of 80,447 women were included in the final analysis.

Measurements

The participants were asked about their general characteristics, including occupations, lifestyle factors, sociopsychological factors, past medical history, family history for medical diseases, surgical history, list of medications and dietary habits. Additionally, the participants were asked about factors associated with obstetrics and gynecology. Women were also asked whether they had ever had a SA; if the answer was ‘yes’, then they were asked at what age the SA had occurred. Additionally, participants were asked about other factors, such as age at menarche, age at first pregnancy, gestational hypertension and gestational diabetes.

Women were asked to recall their weight at age 20 years (surveys from 2004 to 2006) or at age 18 years (surveys from 2007 to 2012). From 2004 to 2006, women had to report their weight at 20 years, but a corresponding question changed to asking the weight at age 18 instead. Therefore, women who participated in the surveys between 2007 and 2012 reported their recalled weight at age 18 only. BMI at age 18 or 20 years was calculated using the measured height at the baseline and dividing the weight by the height squared (kg/m²).

Classification of BMI

We modified the BMI criteria of the Steering Committee of the Regional Office for the Western Pacific Region of the World Health Organization (WHO-WPRO), which the International Association for the Study of Obesity and the International Obesity Task Force had suggested to be the proper categorization of obesity in Asians. The criteria defines ‘underweight,’ ‘normal range,’ ‘overweight at risk,’ ‘obese I,’ and ‘obese II’ as a BMI under 18.5 kg/m², between 18.5–22.9 kg/m², between 23–24.9 kg/m², between 25–29.9 kg/m², and 30 kg/m² or higher, respectively [20]. According to these criteria, people who were either ‘obese I’ or ‘obese II’ comprised only 3% of the study population. For this reason, women who were in either the ‘obese I’ or ‘obese II’ group were placed into one group (‘obese’). For the reference group, the ‘normal range’ group was selected.

Statistical analysis

Multivariable logistic regression was applied to compute odds ratios (ORs) and 95% confidence intervals (95% CI)
of the association between BMI at ages 18–20 years and SA. Possible confounders, such as participants’ age at the survey, income, education, comorbid diseases, exercise, cigarette smoking, alcohol drinking, gestational hypertension and gestational diabetes, were selected based on a literature review. Covariates that altered the odds ratio (OR) for at least one SA in the underweight population by 10% compared to the original model were selected.

Initially, the outcome variable was SA; then, we further defined multiple SAs as variables for those who had more than one SA. First, we analyzed the association between pre-pregnancy BMI and women who ever had an SA. Consequently, women who experienced a SA more than twice were classified as the ‘event group,’ compared to those who never had a SA or experienced a SA only once. Similarly, those who had a SA at least three times were defined as the ‘event group’ in a later analysis. Additionally, we classified these cases by age at first SA to evaluate the effects of BMI across distinct age groups. Women who experienced SA were divided into 3 groups (≤25 years, 26–28 years, and >28 years) by tertile distribution of age at first SA. Additionally, as both BMI and spontaneous abortion showed associations with gestational diabetes [21–23] and gestational hypertension [22, 24], we performed a stratification analysis on the association between BMI and spontaneous abortions according to these two comorbidities to assess a potential effect modifications.

For statistical analysis, SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used. We set P-values less than 0.05 to indicate significance.

Ethics
Written consent was provided by all subjects who agreed to participate in the HEXA. The statistical analysis of publicly available data was approved by the Institutional Review Board of the Seoul National University Hospital in Seoul, Korea (IRB No.1408-087-604).

Results
Women who experienced SA were more likely to have more than a high-school education compared to women without an SA experience (25.2% vs. 23.3%) and had an older age at first pregnancy (≥27 years) than women without SA experience (31.9% vs. 29.3%). The proportion of women who had gestational diabetes (GDM) or gestational hypertension (GHT) also differed between SA and non-SA groups (GDM: 1.18% with SA vs. 0.91% without SA; GHT: 6.0% with SA vs. 4.7% without SA). The proportion of women with babies over 4.0 kg (macrosomia) or under 2.5 kg (micromomia) also differed between the two groups (macrosomia: 8.2% with SA vs. 7.0% without SA; micromomia: 5.6% with SA vs. 3.8% without SA) (Table 1).

In the adjusted logistic regression model, a significantly increased likelihood was observed in women who had a BMI lower than 18.5 kg/m² (OR 1.10, 95% CI 1.05–1.15); conversely, a significantly reduced likelihood of SA was observed in women who had a BMI between 23–24.9 kg/m² (OR 0.94, 95% CI 0.88–0.99) compared to the reference group with a BMI between 18.5–22.9 kg/m². The association between BMI and total SAs showed a U-shape pattern when considering all three SA categories. When we defined multiple SA as women who had at least 3 SA, the likelihood significantly increased in both those who had a BMI less than 18.5 kg/m² and those who had a BMI of 25 kg/m² or higher at ages 18–20 years (OR 1.29, 95% CI 1.14–1.46 and OR 1.39, 95% CI 1.09–1.78, respectively, for three or more SAs) (Table 2).

Different patterns were observed in groups with different ages of onset of SA. In women who had their first SA at the age of 25 years or younger, only those with a BMI of 25 kg/m² or higher at ages 18–20 years showed a significantly increased likelihood (OR 1.22, 95% CI 1.02–1.45) of SA. In contrast, the likelihood of SA at ages 26 to 28 years decreased in women with a BMI of 25 kg/m² or higher (OR 0.82, 95% CI 0.66–1.01). In regard to the likelihood of an SA after the age of 28 years, only women with a BMI less than 18.5 kg/m² at ages 18–20 years showed a marginally significant increased likelihood (OR 1.11, 95% CI 1.02–1.21) (Table 3).

In the stratification analysis of smoking status before first pregnancy, there were similar patterns in the likelihood of SA according to smoking status with various degrees of ORs, compared to the reference group (BMI 18.5–23 kg/m²). In women who did not smoke before pregnancy, the likelihood significantly increased for those who had a BMI less than 18.5 kg/m² (OR 1.09, 95% CI 1.05–1.15) and decreased with marginal significance for those who had BMIs between 23–24.9 kg/m² (OR 0.95, 95% CI 0.89–1.00). In women who smoked before the first pregnancy, those who were ‘underweight’ at ages 18–20 years had an increased odds ratio (OR 1.31, 95% CI 0.70–2.44), whereas the odds ratio in those who had a BMI of 25 kg/m² or over was decreased (OR 0.74, 95% CI 0.15–3.59), although they were not significant (Table 4).

An additional stratification analysis was conducted with gestational diabetes and gestational hypertension. In women with gestational hypertension, only women with BMIs less than 18.5 kg/m² were associated with a higher likelihood of SA (OR 1.22, 95% CI 1.01–1.49). In those with gestational diabetes, no significantly increased OR was observed in the groups, compared with the reference group. Among women with no gestational diabetes and gestational hypertension, both underweight and obesity were associated with a higher likelihood of SA, and women who were in the overweight range
showed significantly decreased likelihoods of SA, which were similar to the patterns observed for the entire population (Additional file 1: Table S1 and Additional file 2: Table S2).

**Discussion**

The goal of this study was to evaluate the effect of pre-pregnancy BMI on SA as an independent risk factor in a large Korean population. In the analysis of approximately 80,000 women, both high and low BMIs showed increased likelihoods of SA, resulting in a U-shaped association. In contrast to the expected result, being overweight (BMI 23–24.9 kg/m2) showed the lowest OR of SA. Our results also showed a similar pattern to the results of a study conducted on more than 1 million Asians, in which a harmful effect due to being underweight and a

| Attained education ≥12 years | Spontaneous Abortion |
|-----------------------------|----------------------|
| No                          |                       |
| Yes                         |                       |
| N (%)                       | N (%)                |
| 14,598 (23.3)               | 4,484 (25.2)         |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 538 (0.859)                                 | 154 (0.865)          |

| Ever consumed alcohol† | Spontaneous Abortion |
|------------------------|----------------------|
| No                     | Yes                  |
| N (%)                  | N (%)                |
| 21,222 (33.9)          | 6,139 (34.5)         |

| Regular exercise | Spontaneous Abortion |
|------------------|----------------------|
| No               | Yes                  |
| N (%)            | N (%)                |
| 32,437 (51.8)    | 9,211 (51.7)         |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Hypertension                     |                      |
| No                               | Yes                  |
| N (%)                            | N (%)                |
| 37 (0.06)                        | 9 (0.05)             |

| Ever consumed alcohol† | Spontaneous Abortion |
|------------------------|----------------------|
| No                     | Yes                  |
| N (%)                  | N (%)                |
| 20 (0.02)              | 3 (0.02)             |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Diabetes                         |                      |
| No                               | Yes                  |
| N (%)                            | N (%)                |
| 20 (0.02)                        | 3 (0.02)             |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Chronic liver disease           |                      |
| No                               | Yes                  |
| N (%)                            | N (%)                |
| 154 (0.25)                      | 35 (0.20)            |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Tuberculosis                    |                      |
| No                               | Yes                  |
| N (%)                            | N (%)                |
| 2,067 (3.30)                    | 587 (3.30)           |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Thyroid disease                  |                      |
| No                               | Yes                  |
| N (%)                            | N (%)                |
| 211 (0.34)                      | 73 (0.41)            |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Medical history before pregnancy | Spontaneous Abortion |
|----------------------------------|----------------------|
| Reproductive factors             |                      |
| Menarche age (years)             |                      |
| ≤14                              |                      |
| 23,559 (37.6)                   | 6,830 (38.4)         |
| 15                              |                      |
| 14,077 (22.5)                   | 3,845 (21.6)         |
| ≥16                             |                      |
| 23,903 (38.2)                   | 6,816 (38.3)         |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Reproductive factors | Spontaneous Abortion |
|----------------------|----------------------|
| First pregnancy age  |                      |
| ≤23                  |                      |
| 19,199 (30.7)        | 5,093 (28.6)         |
| 24–26                |                      |
| 25,066 (40.0)        | 7,029 (39.5)         |
| ≥27                  |                      |
| 18,372 (29.3)        | 5,688 (31.9)         |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Reproductive factors | Spontaneous Abortion |
|----------------------|----------------------|
| First pregnancy outcome |                      |
| Stillbirth           |                      |
| 393 (0.63)           | 178 (1.00)           |
| Extraterine pregnancy |                      |
| 195 (0.31)           | 67 (0.38)            |
| Artificial abortion  |                      |
| 7,467 (12.0)         | 1,466 (8.3)          |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Reproductive factors | Spontaneous Abortion |
|----------------------|----------------------|
| Number of children   |                      |
| 1                    |                      |
| 6,358 (10.2)         | 2,062 (11.8)         |
| 2                    |                      |
| 37,754 (60.8)        | 9,974 (57.0)         |
| 3+                   |                      |
| 17,866 (28.8)        | 5,420 (30.1)         |

| Cigarette smoking before the first pregnancy | Spontaneous Abortion |
|---------------------------------------------|----------------------|
| No                                          | Yes                  |
| N (%)                                       | N (%)                |
| 20 (0.02)                                   | 3 (0.02)             |

| Reproductive factors | Spontaneous Abortion |
|----------------------|----------------------|
| Gestational diabetes |                      |
| 569 (0.91)           | 211 (1.18)           |
| Gestational hypertension |                  |
| 2,966 (4.7)          | 1,065 (6.0)          |
| Macrosomia (>4.0kg)  |                      |
| 4,406 (7.0)          | 1,646 (8.2)          |
| Micosomia (<2.5kg)   |                      |
| 2,390 (3.8)          | 995 (5.6)            |

*p-value from χ²-test
†Due to lack of information about age of beginning of drinking, usual drinkers were included in this category
positive effect due to being overweight (22.6–25.0 kg/m²) on mortality was suggested [25].

Considering the age at the first SA, it appears that a high BMI or being ‘obese’ at ages 18–20 years seems to affect SA at an earlier age, such as 25 years or younger. In contrast, lower BMI at ages 18–20 years or being ‘underweight’ influenced SA at a later age (i.e., more than 25 years). If women had gestational hypertension, those with a BMI under 18.5 kg/m² tended to have more SAs.

As many studies have focused only on the harm of being obese before pregnancy, the possible association between underweight and reproduction has not received much attention. However, our results suggest that underweight women at pre-pregnancy ages are at higher risk for SA compared to normal weight women.

According to the literature review, there is evidence that an increase in BMI raises the risk of SA in the general population [26], as well as in women who have undergone infertility treatment [8]. However, the relationship between lower BMI and SA is far from conclusive, especially in Asians. In a Danish National Birth Cohort (DNBC), 23,000 women were analyzed, and women with a pre-pregnancy BMI under 18.5 kg/m² or higher than 25 kg/m² had an increased hazard ratio (HR) of SA (HR 1.24, 95% CI 0.95–1.63; HR 1.14 95% CI 0.98–1.31, respectively) [10]. In comparison, our results show significantly increased ORs in both ‘underweight’ and ‘obese’ populations, demonstrating a U-shaped pattern.

In regard to the association between BMI and multiple recurrent SA, women with a higher BMI were considered to have a greater likelihood of SA. A study conducted in the Guangzhou Chinese population reported significantly increased likelihoods of recurrent SA in participants with a BMI of 24 kg/m² or higher (OR 1.54; 95% CI 1.28–1.89) compared to their counterparts [27]. Because this study only compared those with a BMI of 24 kg/m² or higher to those with a BMI under 24 kg/m², it was impossible to evaluate the effect of lower BMIs on SA. Another study conducted in the U.K. analyzed 844 pregnancies of 491 women with recurrent SA. In this study, women with a BMI under 19 kg/m² or over 30 kg/m² had increased ORs, but neither group was significant [28].

Given the number of studies regarding the effect of smoking on SA, studies comparing the effect of BMI on both smokers and non-smokers are scarce. Most studies evaluate the effect of smoking and BMI on SA separately [29]. A study conducted in Sweden reported that the interaction among age, BMI and smoking was not statistically significant [29]. However, as seen in our results, the likelihood of SA increases in both ‘underweight’ and ‘obese’ women, and this association is not linear. Additionally, it is well known that as BMI increases, the risk of hypertensive disorders also increases [30]. Interestingly, in

### Table 2 Logistic regression for having spontaneous abortions (SAs) at age 18–20 from the Health Examinees Study (HEXA), 2004–2012

| BMI (kg/m²) | Total women (N=80,447) | Total women with a history of at least | Comparison by groups |
|------------|------------------------|---------------------------------------|----------------------|
|            | One abortion (N=17,180)| Two abortion (N=4,875) | Three abortion (N=1,704) | ≥1 SAs vs. No. SA | ≥2 SAs vs. 0–1 SA | ≥3 SAs vs. 0–2 SA |
| <18.5      | 13128                  | 3,122 (17.5)                        | 896 (18.38)          | 335 (19.7)       | 1.10 (1.05–1.15)  | 1.14 (1.06–1.23)  | 1.29 (1.14–1.46)  |
| 18.5–22.9  | 56692                  | 12,462 (70.0)                       | 3,380 (69.3)         | 1,149 (67.4)     | 1.00 (ref)        | 1.00 (ref)        | 1.00 (ref)        |
| 23–24.9    | 8148                   | 1,675 (9.4)                         | 438 (9.0)            | 148 (8.7)        | 0.93 (0.88–0.99)  | 0.91 (0.82–1.01)  | 0.88 (0.74–1.04)  |
| ≥25        | 2479                   | 551 (3.1)                           | 161 (3.3)            | 72 (4.2)         | 1.06 (0.96–1.16)  | 1.13 (0.96–1.33)  | 1.39 (1.09–1.78)  |

*Adjusted for age, education, smoking before first pregnancy, drinking status and first pregnancy age.

### Table 3 Stratification analyses by maternal age for the likelihood for total and recurrent spontaneous abortion (SA) of body mass index (BMI) at 18–20 years old in the Health Examinees Study (HEXA), 2004–2012

| BMI (kg/m²) | Maternal age |
|------------|--------------|
|            | SA at ≤25 years (N=3,980) | SA at 26–28 years (N=3,977) | SA at >28 years (N=4,321) |
|            | N (%) | OR² (95% CI) | N (%) | OR² (95% CI) | N (%) | OR² (95% CI) |
| <18.5      | 636 (16.0) | 1.07 (0.97–1.17) | 768 (19.3) | 1.17 (1.08–1.27) | 844 (19.5) | 1.11 (1.02–1.21) |
| 18.5–22.9  | 2,765 (69.5) | 1.00 (ref) | 2,761 (69.4) | 1.00 (ref) | 2,989 (69.2) | 1.00 (ref) |
| 23–24.9    | 427 (10.7) | 1.02 (0.91–1.32) | 356 (8.95) | 0.92 (0.82–1.03) | 376 (8.7) | 0.93 (0.83–1.04) |
| ≥25        | 153 (3.8) | 1.22 (1.02–1.45) | 92 (2.3) | 0.82 (0.66–1.01) | 112 (2.6) | 0.96 (0.79–1.17) |

*Only included participants who were enrolled between 2007 and 2012 due to lack of information in age at spontaneous abortion.

*Adjusted for age, education, smoking before first pregnancy and drinking status.
women who had gestational hypertension, we observed significantly increased ORs only in the ‘underweight’ population.

There is abundant evidence supporting the biological plausibility of the extended risk of higher BMIs and the risk of SA. Adolescent or early adult obesity is related to increased overall mortality and especially an increased risk of diabetes and cardiovascular diseases in adult life [31]. The association between obesity in youth and inflammation leads to vascular damage over time. Chronic inflammation may have a key role in SA by damaging the vessels, which support the utero-feto-placental complex [32].

In contrast, there are also studies supporting the mechanism of SA in low BMI women. It has been reported that women with low weights have an increased risk of fetal growth retardation [33], which can be explained by an increased rate of vasoconstriction and decreased serum glucose levels due to poor diet and decreased blood pressure, provoking reduced placental perfusion [34]. Additionally, it has been proposed that leptin, a hormone secreted by adipose cells, may play a role in this association. Underweight women usually have low levels of this hormone, which can block ovulation [35]. Similarly, maternal underweight caused by a shortage of food or eating disorders, such as anorexia or bulimia, is associated with SA [36, 37].

There are several limitations to this study. First, as the original HEXA was designed to mainly focus on other chronic diseases, the recall of retrospective, pregnancy-related information might be less accurate. However, as participants were not aware of the main purpose of this study, there is less chance for recall bias. Additionally, the mean age at enrollment was 52.0 years, and the women were asked to recall their weight nearly 30 years prior. The results of the Nurses’ Health Study (NHS) indicate that participants were able to recall their weight at the age of 18 years, and the correlation coefficient between recalled and objective measurements for weight was approximately 0.9 [38]. Although women in the NHS were aged 25 to 42 years were therefore younger than our participants, there is evidence that self-reported height and weight data are adequate for assessing associations in epidemiological studies [39]. In the stratification analysis of cigarette smoking before pregnancy, we had an insufficient number of samples to explore the effect of the association of first age of smoking and BMI at ages 18–20 years and SA.

This study’s strength is its large size and prospective potential. To the best of our knowledge, it is currently the largest study that has addressed pre-pregnancy BMI and SA. Additionally, although this study used baseline cohort data with cross-sectional analysis, temporal characteristics are included in the analysis, as women with BMIs at ages 18–20 years were analyzed. Reverse causation is the most important problem, in which the loss of weight resulting from particular diseases can falsify the association between lower BMI and health outcomes. To clarify this problem, we excluded women who had pregnancies before the ages of 18–20 years. Furthermore, to provide reliable estimated values for the total effect of BMI on the likelihood of SA in a large Korean population, this study also evaluated the relationship between low BMI and the likelihood of SA in a more discrete way. This particular outcome could not be appropriately demonstrated in most of the earlier studies conducted in European populations.

Conclusions

This study revealed that pre-pregnancy BMI at ages 18–20 years was associated with a higher likelihood of SA in underweight or obese women, using the Asian BMI classification. This U-shaped association was much stronger for recurrent, consequent SA or in women who had ever smoked cigarettes before pregnancy. Age at SA and gestational hypertension modified the association of pre-pregnancy BMI with SA. Obese women had a higher likelihood of SA at earlier maternal ages, whereas underweight women had a higher likelihood of SA at typical or later ages or with gestational hypertension. Further studies are needed to evaluate the exact cause of the difference in age trends and BMI ranges.

Additional files

Additional file 1: Table S1. Stratification analyses by gestational diabetes (GDM) for the likelihood for total and recurrent spontaneous abortion (SA) of body mass index (BMI) at 18–20 years old in the Health Examinee Study (HEXA), 2004–2012. (DOC 33 kb)

Additional file 2: Table S2. Stratification analyses by gestational hypertension (GHT) for the likelihood for total and recurrent spontaneous abortion (SA) of body mass index (BMI) at 18–20 years old in the Health Examinee Study (HEXA), 2004–2012. (DOC 33 kb)
Competing interests
The authors declared that they have no competing interests.

Authors' contributions
Sun Jae Jung (SJ), Sue Kyung Park (SKP) and Daehye Kang (DK) set conception and design of the study. Keun-Young Yoo (KY), Jong-Koo Lee (JKL) and DK helped the acquisition of data.SJJ, SKP and Aeun Shin (AS) made the draft of the manuscript. Sang-Ah Lee (SAL), Ji-yeob Choi (JYC), and Yun-chul Hong (YCH) reviewed the manuscript and revised critical point with SJJ, and AS. All authors read and approved the final manuscript.

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