Effect of pro-inflammatory diet before pregnancy on gestational age and birth weight: The Japan Environment and Children's Study

学　位　論　文

Effect of pro-inflammatory diet before pregnancy on gestational age and birth weight: The Japan Environment and Children's Study

（妊娠前の向炎症食が妊娠週数および出生体重に及ぼす影響：子どもの健康と環境に関する全国調査）

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概要：

早産（PTB）では新生児の未熟性のため罹患率と死亡率の主な原因となる。日本では、医療が発展した現代においても、早産や低出生体重児（LBW）の割合が増加傾向にあり、早産のリスクを軽減するために対策が必要である。

毎日の食事によって誘発される母体の全身性炎症は、早産の重要な原因の１つと考えられている。海外では炎症誘発性の食事（向炎症食）によって全身的なバイオマーカーである高感度の C 反応性タンパク質のレベルが上昇し早産のリスクと関連していると報告された。

近年、食事は慢性炎症の調節に重要な役割を果たすことが分かってきており、向炎症性および抗炎症性の食事療法の概念が報告されている。食事性炎症指数（DII）は、個人の食事の向炎症および抗炎症性を評価する方法であると報告され、肥満、喘息、結腸直腸癌など炎症と関係する疾患との関連が証明されている。

妊娠前の向炎症性/抗炎症性の食事と産科的アウトカムとの関連に関しては、出生コホート研究はほとんど行われていない。今回、大規模な日本の出生コホート研究を用い、DII を計算することで、妊娠期間と出生時体重に対する妊娠前の向炎症性食事の影響を調査した。

材料および方法

研究デザイン

この研究では、2011 年 1 月に開始された政府資金による出生コホート研究である子どもの健康と環境に関する全国調査（JECS）のデータを使用した。 この研究は、環境省の疫学研究機関審査委員会、参加機関の倫理委員会に承認され、また、ヘルシンキ宣言および国内での規制とガイドラインに従った。

このデータは、(1) 医学的背景を含む、妊娠第 1 三半期間前後に得られた自己申告アンケート、または食物摂取頻度アンケート（FFQ） (2) 母の教育状態や世帯収入などの社会経済的地位を含む、第 2 三半期間/第 3 三半期間に収集された自己申告アンケート (3) 各被験者の施設の医療記録から得られた産科のアウトカム（4）妊娠初期の母体の血液サンプルの 4 種類の情報で構成されている。また、 FFQ は妊娠前の情報である。

食事性炎症指数（DII）の計算

食事性炎症指数（DII）は、2014 年に Shivappa らによって開発された、毎日の食事が炎症性もしくは抗炎症性であるかの包括的な指標である。DII の値が大きいほど、炎症誘発性の食事、負の値が大きいほど、抗炎症食であることを示す。

各対象者の FFQ からカロリー、炭水化物、タンパク質、総脂肪、アルコール、繊維、コレステロール、飽和脂肪酸、一価不飽和脂肪酸（MUFA）、多価不飽和脂肪酸（PUFA）、脂肪酸（n-3 および n-6 FA）、

ナイアシン、チアミン、リボフラビン、鉄、マグネシウム、亜鉛、セレン、ビタミン A、B-12、B-6、C、D、E、葉酸、β-カロチン、ニンニク、ショウガ、タマネギの 30 品目について摂取量の情報を得た。各対象者の DII スコアは、Shivappa らに従って計算した。

産科的アウトカム

早産は、妊娠 37 週間未満と妊娠 34 週間未満に、 低出生体重児は、2500 g 未満と 1500 g 未満の 2 つのカテゴリーにそれぞれ分類した。胎児の成長制限（SGA）は、在胎週数に対しての成長を評価した。また、妊娠高血圧症候群（HDP）と白血球増加症についても検討した。

統計分析

PTB、LBW、SGA、および HDP の調整オッズ比（aOR）および 95%信頼区間（CI）は、多重ロジスティック回帰モデルを使用して計算した。

結果

対象者 89,329 人の DII の範囲は-6.16～+5.80 であり、得られた DII を四分位数に従って分類した（Q1 は最も抗炎症性のカテゴリー、Q4 は最も炎症性の高いカテゴリー）。DII のカテゴリー（Q1～Q4）で、年齢、妊娠前の BMI、妊娠中の喫煙、母親の教育状態、および年間世帯収入に有意差があった（$p < 0.01$）。母親の年齢が 20 歳未満では、最も高い DII のカテゴリー（最も炎症性の高い；向炎症食カテゴリー）の割合が最も多かったが、40 歳以上では、最も低い DII のカテゴリー（最も炎症性の低い；抗炎症食カテゴリー）の割合が最も多かった。DII の四分位数の増加に伴い（向炎症食カテゴリー）、母親の低教育（<10 年）と低世帯収入（<2,000,000 円）の割合が増加した。白血球増加は、DII カテゴリーが大きくなるごとに増加した。産科的アウトカムに関して、 2500 g 未満の LBW および HDP の発生に有意差が見られた（それぞれ $p = 0.03$ および $p = 0.04$）。これらの発症は、DII カテゴリーが大きくなるとともに増加した。

Q1（抗炎症食カテゴリー）と Q4（向炎症食カテゴリー）を比較すると、Q4 では妊娠 34 週未満の早産（aOR : 1.37、95%CI : 1.08-1.73 ）、2500 g 未満の LBW（aOR : 1.15、95%CI : 1.05-1.26）、HDP（aOR : 1.27、95%CI : 1.09-1.36）のリスクが上昇することが示された。

考察

本研究は、日本で最大の出生コホート研究を使用して、炎症性の食事と産科的アウトカムの関係を調査する最初の研究である。私たちの結果は、妊娠前の炎症誘発性の食事が妊娠 34 週未満の早産、2500 g 未満の LBW、HDP の危険因子であることを示唆している。

妊娠前の炎症誘発性の食事と早産との関連のメカニズムは解明されていない。向炎症食が早産を引き起こす経路が 2 つ考えられる。まず、大量の飽和脂肪およびトランス脂肪を含む食品により炎症性サイト

カインを誘導され、プロスタグランジン（PG）とマトリックス分解酵素が生成される。 PG は子宮収縮を刺激し、マトリックス分解酵素は胎児膜を早期破裂させ、自然早産をもたらす。動物研究でも高脂肪食が腸内細菌叢を変化させ、妊娠マウスの子宮に発現する早産抑制メカニズムの調節不全を引き起こすことで早産をもたらすことや、腸内細菌叢の異常が全身性炎症に寄与することが報告されている。したがって、向炎症食群の白血球の有意な増加をもたらす全身性炎症は早産に関連していると推測される。また、習慣的な向炎症食は、アテローム発生プロセスと内皮機能障害につながる。アテローム発生プロセスと内皮機能不全は、高血圧性障害の病因に大きな役割を果たしている。それらの障害が SGA または HDP を引き起こし、医学的介入によってもたらされた人工早産となる可能性がある。したがって、妊娠 34 週未満の早産増加は、HDP（向炎症食習慣によって誘発される心血管イベント）になど対する医学的介入によってもたらされた人工早産の増加による可能性がある。

結論として、妊娠前の向炎症食習慣は PTB、LBW、HDP の危険因子であることがわかった。私たちの研究は、食習慣が産科的アウトカムに影響を与える可能性があることを示唆している。したがって、周産期の予後を改善するために、炎症誘発性の食事を管理する必要がある。

略語(abbreviation)：

JECS, Japan Environment and Children's Study; DII, diet derived inflammation index; FFQ, food frequency questionnaire; PTB, preterm birth; LBW, low birth weight; aOR, adjusted odds ratio; CI, confidence interval; HPC, 17-hydroxyprogesterone caproate; DII, dietary inflammatory index; MUFAs, monounsaturated fatty acids; ;PUFAs, polyunsaturated fatty acids ; FAs fatty acids; SD, standard deviation; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha ; IL, interleukin; SGA, small for gestational age ; HDP, hypertensive disorder of pregnancy ; WBC, white blood cell; BMI, body mass index; PG, produce prostaglandin

序論(introduction)：

Preterm birth (PTB), which can result in low birth weight (LBW) infants, is a major cause of neonatal morbidity and mortality. As preterm infants have immature fetal growth, complications such as cerebral hemorrhage and respiratory distress syndrome can occur (Altman et al., 2011). In Japan, PTB is a public concern because there was an increase in the rate of PTB before 37 weeks (4.5% to 5.6 %), LBW < 2,500 g (6.5% to 9.5 %), and < 1,500 g (0.53% to 0.75%) from 1990 through

2015 (Japanese Ministry of Health, Labor and Welfare 2015). Since the randomized control study by Meis et al (2003), the effectiveness of intramuscular 17-hydroxyprogesterone caproate (HPC) for preventing PTB has been widely recognized worldwide. Despite the widely recognized effectiveness of 17-HPC on recurrent spontaneous PTB, this drug also has potential problems, including lack of effectiveness, for patients without any history of previous spontaneous PTB and pricing concerns (Nelson DB et al., 2017). Therefore, other measures to reduce the risk of PTB that can be applied to a wide range of pregnant women are required.

One of the main causes of PTB is local inflammation in the uterus (Kyozuka et al., 2017). Intrauterine inflammation is thought to be mainly due to bacterial ascending infection from the vagina, resulting in spontaneous PTB (Romero et al., 1988). A recent study indicated that maternal infection is not required for PTB. Maternal systematic inflammation induced by daily diet is thought to be another cause of PTB. A previous randomized control study of Norwegian women showed that intervention during the second trimester by controlling diet or anti-inflammatory diet reduced the risk of PTB (Khoury et al., 2005). Scholl et al. (2011) reported that higher levels of sensitive C-reactive protein, which is a systematic biomarker induced by inflammatory diets, was associated with the risk of preterm delivery.

In non-pregnant adult, diet is thought to play an important role in the regulation of chronic inflammation. For example, a high calorie, high fat diet, such as diets including Western food, promotes inflammation and consumption of Western food exposes the body to repeated inflammation (Lopez-Garcia et al., 2004). As a result, several diseases such as cardiovascular disease, diabetes mellitus, thrombosis, asthma, and depression may occur (Giugliano et al., 2006; Pearson et al., 2003; Ramallal et al., 2015). On the other hand, there are many vegetables and foods rich in minerals, such as traditional Japanese food and Mediterranean food that have a lower inflammatory effect (Guo et al., 2012; Tada et al., 2011). In recent years, the concept of pro-inflammatory and anti61 inflammatory diets has been reported. The dietary inflammatory index (DII) is a method to assess the inflammatory potential of an individual's diet (Shivappa et al., 2014a). The DII has been proved to associate with well-known inflammation related condition such as obesity (Ruiz-Canela M et al., 2015), asthma (Wood LG et al., 2015), and colorectal cancer (Jayedi A et al., 2018).

Although numerous studies have examined the relation between daily diet and occurrence of several diseases, few large birth cohort studies have been conducted with regard to the correlation between the pro/anti inflammatory contents of daily diets before pregnancy and obstetrical complications.

Hence, we investigated the effect of a pro-inflammatory diet before pregnancy by mean of DII score on gestational age and birthweight in the largest Japanese birth cohort study.

方法（materials and methods/procedures）:

Study design

In this study, data from the Japan Environmental Children's Study (JECS), a government-funded birth cohort study started in January 2011, were used. This survey investigated the effect of several environmental factors on children's health (Kawamoto et al., 2014). Eligibility requirements of JECS participants (mothers) were as follows: (1) living in the study area at the time of application and were expected to live in Japan in the near future; (2) expected delivery date between August 1, 2011, and mid-2014; and (3) could participate without difficulty (i.e., they could answer the self-management questionnaire). The target recruitment rate was >50% of all eligible mothers. Written informed consent was obtained from all participating women.

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions. The JECS was conducted in accordance with the Helsinki Declaration and other nationally valid regulations and guidelines.

Data collection

We used the dataset released in June 2016 (dataset: jecs-ag-20160424) for this study. This data set consisted of 4 types of information: (1) Self-reported questionnaire obtained around the 1st trimester, including the medical background, or food frequency questionnaires (FFQs); (2) Self-reported questionnaire collected during their second/third trimester, including socioeconomic status such as maternal education or household income: (3) Obstetrics outcome which was retrieved from medical records of each subject's institution. (4) Maternal blood sample collected during their first trimester. The FFQ was completed during the first trimester, and diet intake was assessed before pregnancy. This tool, which was used in the JECS, has been validated as a self108 administrated diet questionnaire in previous Japanese epidemiological studies (Yokoyama et al., 2016).

In the present study, we excluded cases with insufficient data, multiple pregnancies, or delivery before 22 weeks.

Calculation of dietary inflammatory index (DII)

The dietary inflammatory index (DII) score is a comprehensive indicator of daily inflammatory and anti-inflammatory meal contents developed by Shivappa et al. (Shivappa et al., 2014a). The greater the DII score, the more pro-inflammatory diet. A more negative value indicates a more anti-inflammatory diet.

In the present study, the 30 food parameters, including energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), fatty acids (n–3 and n–6 FAs), niacin, thiamin, riboflavin, iron, magnesium, zinc, selenium, vitamin A, B-12, B-6, C, D, E, folic acid, ß-carotene, garlic, ginger, and onion were obtained from each participants' FFQ. The DII score of each participant was calculated according to Shivappa et al. (2014a). First, the dietary data were linked to a worldwide database that provided a robust estimate of the mean and standard deviation (SD) for each parameter included in the DII (Shivappa et al 2014a). The Z score was calculated by subtracting the standard global mean from the reported amount and dividing the result by the SD. The Z scores were not normally distributed (right skewing); thus, the Z score of each value was converted to a centered percentile score. Then, the centered percentile score for each food parameter was multiplied by the respective food parameter effect score (obtained by reviewing a total of 1943 research articles to determine the relationship between the food parameters and inflammation, as well as by scoring) to obtain a food parameter-specific DII score, which were all summed to create the overall DII score for each participant. DII = I1 · P1 + I2 · P2 + … + I30 · P30, where I is the food parameter effect score considering the effect of inflammation obtained from reviewed research articles, and P is the food specific centered percentile score derived from food data. The DII minimum/maximum in non1 pregnant populations is reported to range from −8.87 to +7.98 (Shivappa et al., 2014a). DII score has already been validated in non-pregnant adults to correlate with various inflammatory markers including C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin (IL)-6 (Shivappa et al., 2014b; Shivappa et al., 2017).

Obstetrics outcomes, and confounding factors

PTB was classified into two categories: delivery before 37 weeks and before 34 weeks. LBW was also categorized into two categories: <2500 g and <1500 g. Fetal growth restriction was evaluated using small for gestational age (SGA). SGA was defined as a birth weight below -1.5 standard deviation (SD) corrected for gestational age and sex according to the "New Japanese neonatal anthropometric charts for gestational age at birth" (Itabashi et al., 2014). In this study, hypertensive disorder of pregnancy (HDP) was defined the new onset of hypertension (≥140/90 mmHg) after the 20th

gestational week in a previously normotensive woman. Leukocytosis was defined as a white blood cell (WBC) count of >12,000 in the maternal blood sample. Confounding factors for this study were determined by clinical importance, i.e., those believed to be related to PTB and dietary habits. The following items were used as confounding factors: maternal age, maternal BMI before pregnancy, maternal smoking status, education state of mother, and annual household income. Maternal age was categorized into six age groups:≤19, 20-24, 25-29, 30-34, 35-39, and ≥40 years. Maternal body mass index (BMI) before pregnancy was calculated by dividing the height (m) by the square of the body weight (kg) using the height and weight. We categorized participants into three BMI groups as follows: <18.5, 18.5-25.0, and≥ 25.0 Kg/m2. T1 data provided information on their smoking status during first trimester: "never smoked," "quit smoking before pregnancy," "quit smoking during early pregnancy," and "kept smoking during pregnancy." "Kept smoking during pregnancy" was defined as the smoking category; otherwise it was defined as non-smoking. Maternal education was categorized into four groups (junior high school: <10, high school: 10-12, professional school or university: 13-16, and graduate school: ≥17 years). Annual household income was categorized into four levels (<2,000,000; 2,000,000-5,999,999; 6,000,000-9,999,999; and ≥10,000,000 JPY) (Kyozuka et al., 2019).

Statistical analyses

The participants were categorized according to quartiles (Q1 was for the most anti- inflammatory group and Q4 for the most pro-inflammatory group). Maternal characteristics were summarized according to each group. One-way analysis of variance and the chi square test was used to compare the continuous and categorical variables, respectively. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) for PTB, LBW, SGA and HDP were calculated using a multiple logistic regression model, accounting for maternal age, maternal BMI before pregnancy, maternal education, maternal smoking status, and household income. We accomplished this by using dummy variables for categorical variables composed of more than three categories. SPSS version 21 (IBM Corp., Armonk, NY) was used for the statistical analyses. A p value <0.05 indicated statistical significance.

結果(results) :

The total number of fetal records from infants delivered between 2011 to 2014 in the JECS was 104,102. Of these, 3,332 and 982 infants were excluded due to insufficient data for DII and multiple gestation, respectively. Then, 609, 1,085, and 8,775 participants were excluded for the reasons of abortion, unknown gestational age, and insufficient data, respectively. After applying our inclusion

criteria, 89,329 participants were eligible for the present study and categorized into 4 groups according to quartiles (Figure 1). Figure 2 shows the frequency distribution of the DII score. The DII score ranged from -6.16 to +5.80.

Maternal medical and socioeconomic background and obstetric outcomes

Table 1 summarizes the maternal medical background and obstetric outcomes according to quartiles for DII score. There was a significant difference in age, BMI before pregnancy, smoking during pregnancy, maternal education, and household income among the four groups ($p<0.01$). While maternal age < 20 years was the most common in the highest DII score quartile (the most pro-inflammatory group), maternal age > 40 years was the most common in the lowest DII score quartile (the most anti-inflammatory group). The proportion of low maternal education (<10 years) and low household income (<2,000,000 yen) increased with increasing quartiles of DII. The ratio of leukocytosis, which was defined as WBC count over 12,000 during the first trimester, also increased with each increasing quartile of DII. With regard to obstetrics outcome, significant differences in the occurrence of LBW < 2500 g and HDP were seen ($p=0.03$ and $p=0.04$, respectively). These occurrences increased with the increase in DII category.

DII and risk of obstetric complication

Table 2 summarizes the association between DII category and risk of obstetric complications (PTB, LBW, SGA, and HDP). When we considered Q1 (the most anti-inflammatory groups) as reference, multiple logistic regression showed that Q4 (the most pro-inflammatory group) had an increased risk of PTB <34 weeks (aOR: 1.37, 95% CI: 1.08-1.73), LBW <2500 g (aOR: 1.15, 95% CI: 1.05-1.26), and HDP (aOR: 1.27, 95% CI: 1.09-1.36).

考察(discussion)：

This is the first study to investigate the relationship between inflammatory diet and obstetric outcomes, using the largest birth cohort study in Japan. Our results suggest that pro-inflammatory diet before pregnancy was a risk factor for PTB <34 weeks and LBW <2500 g, and HDP. Until now, few studies that examined the correlation between DII score during pregnancy and obstetrics outcomes have conducted. Sen et al. (2016) calculated the DII score during pregnancy using 28 dietary parameters and examined the association between the quartile of DII score and obstetric outcomes in 1808 maternal participants. They reported that a pro-inflammatory diet during

pregnancy was associated with maternal systematic inflammation and may be associated with fetal growth restriction. Our result that pro-inflammatory diet before pregnancy is related to maternal systematic inflammation in term of leukocytosis (defined WBCs >12,000) is consistent with the findings of that study. Contrary to that study, our study indicates that pro229 inflammatory diet before pregnancy is associated with PTB < 34 weeks, LBW < 2500 g, and HDP but not with growth restriction. We assumed that the reasons for these discrepancies are the differences in sample size, definition of obstetrics outcome, assessment time of diet content (during or before pregnancy), and statistical methods for calculating the risk of obstetrics outcomes. In the present analysis, we applied quartiles of DII as dummy variable, leaving the Q1 group (the most anti-inflammatory diet) as reference to calculate the aOR of each DII category (Q2, Q3, and Q4) for obstetrics outcomes in the logistic regression model. We thought that this logistic model enabled the evaluation of the risk of adverse obstetrics outcomes in every category of participants.

The mechanism of the association between pro-inflammatory diet before pregnancy and PTB is unknown. We think there are two scenarios where pro-inflammatory diets cause PTB. First, some foods with large amounts of saturated and trans-fats induce pro- inflammatory cytokines (Soto-Vaca et al., 2013). Pro-inflammatory cytokines, such as interleukin (IL) and tumor necrosis factor (TNF), produce prostaglandin (PG) and matrix-degrading enzymes. PG stimulates uterine contractions whereas degradation of the extra cellular matrix leads to preterm rupture of fetal membranes, resulting in spontaneous PTB. In animal studies, Manuel et al (2019) reported that a high fat diet leads to gut dysbiosis and dysregulated uterine expression in pregnant mice, resulting in PTB. They also reported immune tolerance induced by endotoxin priming prevents high-fat diet dams from PTB (Manuel CR et al., 2019). Other studies reported that alterations in the composition and function of gut microbiota, such as dysbiosis, contribute to systematic inflammation (Laugerette et al., 2011). Therefore, it might be reasonable to assume that systematic inflammation as a significant increase in white blood cells in the pro-inflammatory diet group was related to PTB. However, PTB has the same endpoint, consisting of two clinical subtypes: spontaneous PTB and medically indicated PTB, which is conducted for cases of SGA or HDP (Kyozuka et al, 2018). Habitual pro-inflammatory diet has associations with regulation of inflammation, leading to modulation of the atherogenesis process and endothelial dysfunction (Barbareslo J, et al. 2013). The atherogenesis process and endothelial dysfunction play a major role in the pathogenesis of hypertensive disorder (Roberts, J.M., et al. 1993 and (Ramallal, R, et al. 2015). Therefore, we speculate another scenario for the increase in PTB < 34 weeks among the pro-inflammatory group; this might be due to an increase in medically indicated

PTB, such as HDP (a cardiovascular event induced by pro-inflammatory diet habits).

The strength of this study is that it is the first-large-scale study conducted in Japan by the Japanese government with meticulous attention to data collection. Therefore, this study is considered to be representative of the general pregnant population in Japan (Yamaguchi et al., 2018). Nevertheless, this study also has potential limitations to be considered. First, although we measured the white blood cell during first trimester, we did not measure or include data on plasma inflammatory cytokines, such as CRP, IL-6, TNFα, or another inflammation marker in the present study. This data could augment the correlation between pro-inflammatory diet and PTB. Second, although we accounted for some confounding factors in large portions of the questionnaire, unknown factors which may affect the occurrence of PTB, LBW, or HDP might have existed. Third, the DII score of each participant in the present study was calculated using only the FFQ of JECS participants who were Japanese women and not validated to other ethnics yet. Therefore, our results may not be applicable to other ethnicities. Fourth, because the FFQ used for calculating the DII score in the present study was based on self-reported information during their first trimester, recall bias may pe possible as participants might have had morning sickness and were asked to recall their diet content before pregnancy.

In conclusion, we found that a pro-inflammatory diet before pregnancy was a risk factor for PTB, LBW, and HDP. Our study suggests that dietary habits may affect obstetric outcomes. Therefore, pro-inflammatory diet needs to be controlled to improve perinatal prognosis.

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All authors approved the final manuscript. M.I. initiated the concept and designed the study to which H.K., A.Y., K.F., and K.H. gave advice. M.K., A.S., and Y.O., collected the data. M.I. analyzed the data and wrote the manuscript. M.H., K.F., S.Y., M.K., A.S., Y.O., K.H., and JECS group reviewed the manuscript and gave critical advice.

図説明(figure legends):

Figure 1. Study enrollment flowchart

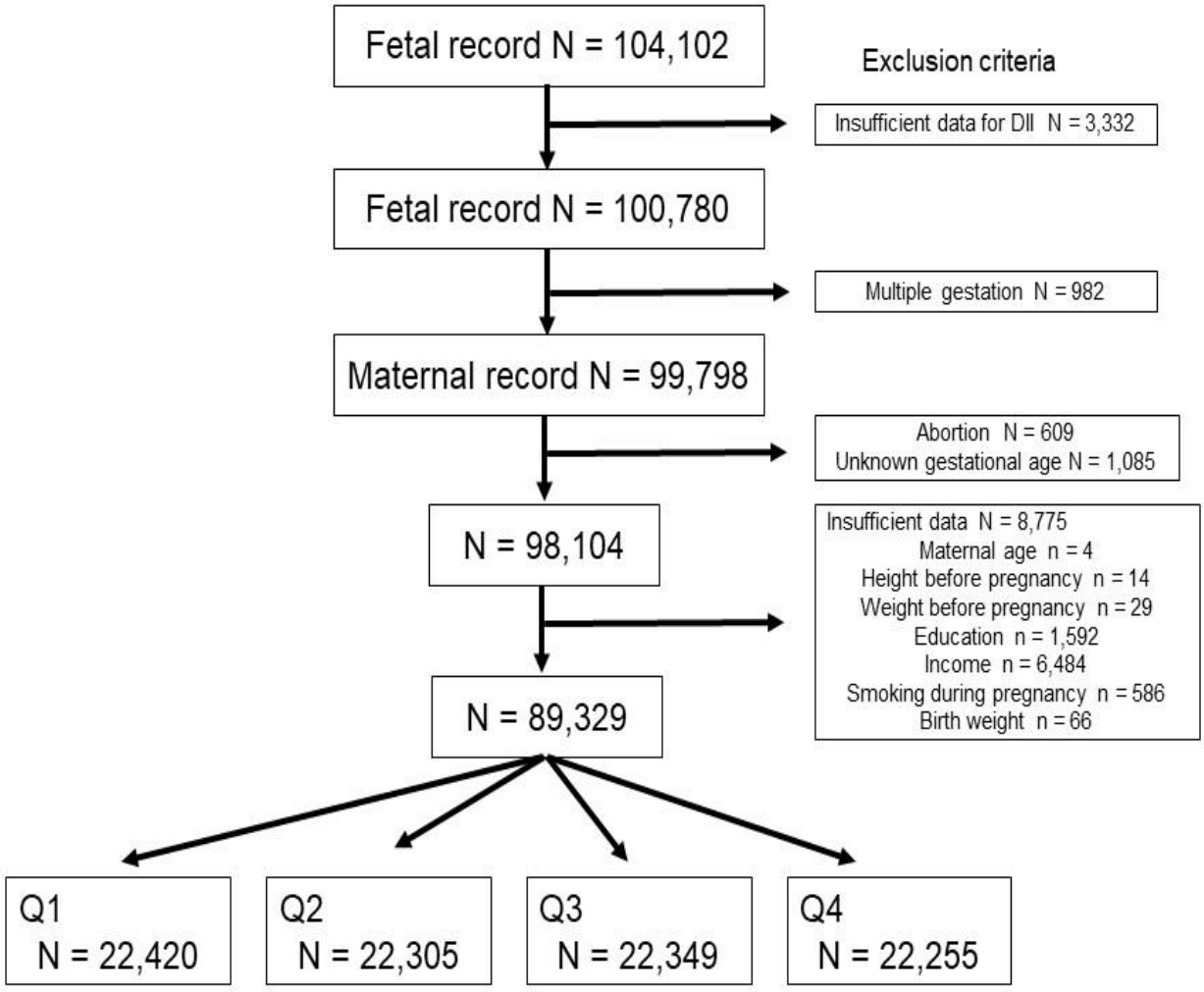

Figure 2. The frequency distribution of DII score

The horizontal axis indicates DII score and the vertical axis indicates the number of participants. DII score ranged from -6.16 to 5.80. The curved line indicates the normal distribution curve.

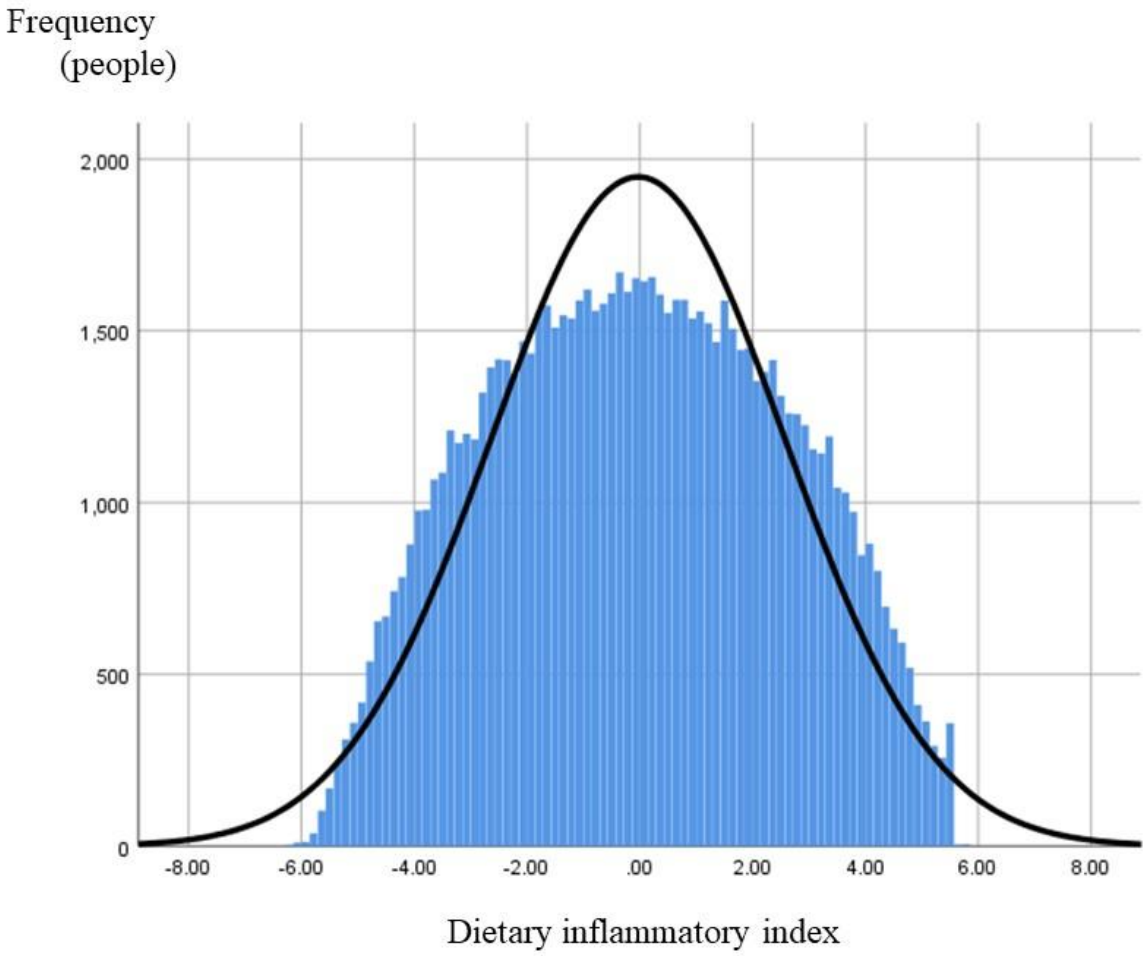

Table 1. Maternal medical background and obstetric outcomes

Variable	Quartile for DII				p-value
	Q1 (n=22,420) most anti-inflammatory	Q2 (n=22,350)	Q3 (n=22,349)	Q4 (n=22,255) most pro-inflammatory	
Maternal medical background					
DII before pregnancy	-3.41 (0.90)	-1.04 (0.58)	0.96 (0.59)	3.37 (0.91)	< 0.01[a]
Maternal age, years mean (SD)	32.1 (4.8)	31.7 (4.9)	31.1 (4.9)	29.8 (5.3)	< 0.01[a]
Maternal age category, years %					
<20	0.3	0.5	0.5	1.2	
20 - 24	4.9	6.2	8.1	13.7	
25 - 29	23.8	25.6	28.5	32.7	< 0.01[b]
30 - 34	38.0	37.4	36.5	32.0	
35 - 39	27.2	25.2	22.1	17.2	
>40	5.8	5.2	4.3	3.2	
BMI before pregnancy (kg/m^2), %					
<18.5	14.9	15.9	16.3	16.8	
18.5 to 25.0	74.4	74.2	73.6	71.7	< 0.01[b]
>25	10.7	9.9	10.2	11.5	
Smoked during pregnancy, %	3.7	3.8	4.5	6.4	< 0.01[b]
Maternal education, year, %					
<10	3.3	3.5	4.4	6.8	
10-12	25.9	27.7	31.1	38.0	

13-16	44.8	43.5	42.3	38.8	< 0.01[b]
≥17 years	26.0	25.3	22.2	16.4	
Household income, JPY, %					
<2,000,000	5.0	4.5	5.2	7.8	
2,000,000-5,999,999	65.6	66.6	67.9	70.4	
6,000,000-9,999,999	24.0	24.2	22.8	18.8	< 0.01[b]
≥10,000,000	5.3	4.7	4.1	3.0	
Gestational week at blood collection, week mean (SD)	11.14 (1.82)	11.10 (1.81)	11.09 (1.83)	11.12 (1.83)	< 0.01[a]
White blood cells, count/L mean	8009 (1927)	8016 (1935)	8057 (1937)	8076 (1936)	< 0.01[a]
White blood cells > 12,000 count/L, %	2.6	2.5	2.9	3.0	0.02[b]
Obstetric outcome					
PTB <37 weeks, %	5.0	4.9	5.2	5.0	0.65[b]
PTB <34 weeks, %	1.0	1.0	1.0	1.2	0.13[b]
LBW <2500 g, %	8.3	8.2	8.7	8.9	0.03[b]
LBW <1500 g, %	0.6	0.5	0.6	0.6	0.38[b]
SGA, %	5.2	4.8	4.9	5.2	0.10[b]
HDP, %	2.7	2.8	2.8	3.1	0.04[b]

DII: dietary inflammatory index, SD: standard deviation, BMI: body mass index, JPY: Japanese Yen, PTB: preterm birth, LBW: low birthweight, SGA: small for gestational age, HDP: Hypertensive disorder of pregnancy

[a] p-value, one-way analysis of variance

[b] p-value, chi-square test

[c] White blood cell count is consist with the number of 19,952, 199,78, 20,116 and 20,156 for Q1, Q2, Q3 and Q4, respectively