Time course of metabolic status in pregnant women: The Japan Environment and Children’s Study

Hatoko Sasaki1*, Naoko Arata1, Ai Tomotaki1,2, Kiwako Yamamoto-Hanada1, Hidetoshi Mezawa1, Mizuho Konishi1, Kazue Ishitsuka1, Mayako Saito-Abe1, Miori Sato1, Minaho Nishizato1, Hirohsa Saito1, Yukihiro Ohya1, Japan Environment and Children’s Study (JECS) Group‡

1National Center for Child Health and Development, Tokyo, Japan, and 2National Center for Global Health and Medicine/National College of Nursing, Tokyo, Japan

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*Correspondence
Hatoko Sasaki
Tel.: +81-3-3416-0181
E-mail address: sasaki-ht@ncchd.go.jp

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ABSTRACT
Aims/Introduction: We aimed to evaluate the metabolic status of pregnant women by assessing metabolic biomarkers of participants in the Japan Environment and Children’s Study, a nationwide, multicenter, pregnancy and birth cohort.

Materials and Methods: Pregnant women aged 14–50 years were studied in 15 centers across Japan. Clinical information was obtained using self-administered questionnaires. Blood samples were taken during the first two trimesters to measure metabolic biomarkers. Samples were divided into seven groups according to the weeks of pregnancy.

Results: Among 82,972 pregnant women, 43 had only type 1 diabetes, 78 had only type 2 diabetes, 2,315 had only gestational diabetes and 354 had only dyslipidemia. Glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol and triglyceride across all the percentiles increased as prepregnancy body mass index increased, whereas high-density lipoprotein cholesterol levels across all the percentiles decreased as body mass index increased. Glycated hemoglobin was high in participants with type 1 diabetes or type 2 diabetes only, but not in those with gestational diabetes or hyperlipidemia only. Participants with type 2 diabetes or dyslipidemia only had high triglyceride in the first trimester, which then decreased in the second trimester. Participants with type 2 diabetes only also showed low high-density lipoprotein cholesterol, whereas participants with dyslipidemia only showed high total cholesterol and low-density lipoprotein cholesterol throughout.

Conclusions: Metabolic biomarkers were affected by blood sample timing and underlying metabolic disease. The Japan Environment and Children’s Study will clarify the influences of metabolic status during pregnancy on the health and development of the offspring in future studies.

INTRODUCTION
The glucose and lipid metabolism of women is known to change during pregnancy. Insulin resistance increases during pregnancy because of an increased secretion of hormones, such as placental growth hormone, that promote the transplacental transport of glyconutrients to the fetus1. Because pregnant women use lipids as an energy source, the plasma levels of cholesterol and triglyceride in pregnant women are relatively high2. In contrast, earlier research has suggested that the timing of blood collection during different stages of pregnancy is an important point to consider. Because of the changes in lipid profile during the second and third trimesters, other factors including pregnancy-related complications and/or placenta dysfunction might impede interpretation regarding cause or consequence3. Pregnant women with obesity are at risk of many complications, including stillbirth, large-for-gestational-age infants and associated complications at birth4. Children born to...
women with higher maternal prepregnancy Body mass index (BMI) and excess gestational weight gain could themselves be at risk of childhood obesity. Identifying women at risk allows initiation of risk-specific treatment and tailored care during pregnancy.

In the present study, we analyzed data collected from pregnant women who participated in a nationwide birth cohort study (the Japan Environment and Children’s Study [JECS]), using a questionnaire and blood samples taken during the first or second trimester of pregnancy, to evaluate their metabolic status. This is the first study to describe the metabolic status of a large cohort of pregnant women aged 14–50 years and living in Japan.

**METHODS**

**Overview**

The JECS is a prospective nationwide birth cohort study that was launched by the Japanese Ministry of the Environment. The JECS covers a wide geographical area of Japan and comprises 15 regional centers (Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka and South Kyushu/Okinawa). Participants were pregnant women and their partners who were recruited during their early pregnancy from hospitals or local government offices when the maternal and child health handbook was provided. The main aim of the JECS was to evaluate whether environmental factors, such as chemicals, physical activity and lifestyle, influence childhood health. The health of mothers reflects genetic factors and lifestyle, and one of the important themes of the study is to establish how the health of mothers during pregnancy affects the subsequent health of their child. Recruitment began in January 2011, and the number of pregnant women enrolled reached 100,000 in March 2014.

Participating children are expected to remain in the study until they reach 13 years of age.

**Ethical approval**

The JECS was carried out based on the Ethical Guidelines for Epidemiological Research published by the Japanese Ministry of Health and Welfare (now the Ministry of Health, Labor and Welfare). The JECS protocol was reviewed and approved by the Japanese Ministry of the Environment’s Institutional Review Board on Epidemiological Studies and the Ethics Committees of all the participating institutions. Written informed consent was obtained from all participants.

**Recruitment**

The eligibility criteria for participants in the JECS were as follows: (i) the participant should reside in the study area at the time of recruitment and expect to continue to reside in Japan for the foreseeable future; (ii) their expected delivery date should be between 1 August 2011 and mid-2014; and (iii) the participant should be capable of participating in the study without difficulty; that is, they must be able to understand the Japanese language and complete the self-administered questionnaire.

Either or both of the following two recruitment protocols were applied: (i) recruitment at the time of first prenatal examination at cooperating health care providers such as obstetric facilities, and/or (ii) recruitment at local government offices issuing pregnancy journals, namely Mother-Child Health Handbooks (the Mother-Child Health Handbook is an official booklet that all expecting mothers in Japan are given complimentary when they become pregnant in order to receive municipal services for pregnancy, delivery and childcare). The study population contained 104,102 fetal records.

**Assessment of clinical information**

Information about the week of pregnancy was obtained from pregnant participants using an initial self-administered questionnaire during the second or third trimester of pregnancy. The height and weight of each mother before pregnancy and the maternal age at registration were obtained either from the participant’s doctors or from a self-administered questionnaire. The lifetime prevalence of diabetes and other endocrine disorders, including complications of type 1 diabetes, type 2 diabetes, gestational diabetes (GDM) and dyslipidemia, was also assessed based on the diagnoses made by the participant’s doctors and the initial self-administered questionnaire.

Screening tests for all pregnant women for GDM and “overt diabetes in pregnancy” are carried out in Japan, using the following stepwise method:

1. Measure random blood glucose level in the first trimester (each hospital should determine its own cut-off value). Before planning a 75-g oral glucose tolerance test for women with a random blood glucose level of 200 mg/dL, check: (i) fasting plasma glucose 126 mg/dL; (ii) glycated hemoglobin (HbA1c) 6.5%, expressed as National Glycohemoglobin Standardization Program value; and (iii) definite diabetic retinopathy for differential diagnosis of “overt diabetes in pregnancy.”

2. Give the pregnant woman a 50-g glucose challenge test (cut-off value 140 mg/dL) or measure the random blood glucose level a second time (cut-off value 100 mg/dL) between 24 and 28 gestational weeks in women not diagnosed as having GDM or “overt diabetes in pregnancy.”

3. A 75-g oral glucose tolerance test is given to all women with a positive screening test result, except women diagnosed as having “overt diabetes in pregnancy” and GDM is diagnosed with International Association of Diabetes and Pregnancy Study Groups criteria. “Overt diabetes in pregnancy” is classified as type 2 diabetes.

The screening method for GDM described in the guideline was also used at the time the present study was carried out. It is reported that the prevalence of GDM was approximately 8.5% when the 75-g oral glucose tolerance test was given to all pregnant women.
Biomarker assays
Non-fasting blood samples were obtained from pregnant women during their second or third trimester of pregnancy. The following biomarkers were assayed by a contract clinical laboratory (SRL, Inc., a commercial laboratory in Tokyo, Japan): HbA1c (National Glycohemoglobin Standardization Program) was measured using a high-performance liquid chromatographic method; serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were analyzed enzymatically using a 7700 clinical chemistry/immunoassay hybrid analyzer (Hitachi High-Technologies Co., Ltd, Tokyo, Japan).

Exclusion of study participants
We prespecified that pregnant participants whose data for HbA1c, Hb, TC, LDL-C, HDL-C or TG were missing or below the quantifiable range in the transcripts of medical records would be excluded. Participants who had missing data or results outside the reference range for other variables, or those who had other endocrine disorders, were also excluded from subsequent analyses.

Statistical analysis
We used the data from individuals in the first and second trimesters with no missing values. The distribution of each biomarker was summarized according to the prepregnancy BMI and maternal age at registration, according to the week of pregnancy (the first trimester was divided into 4–7, 8–11 and 12–13 weeks, and the second trimester into 14–15, 16–19, 20–23 and 24–27 weeks), and according to the presence or absence of diabetes or other endocrine disorders. Each woman was evaluated only once during pregnancy. Each biomarker was summarized using the 2.5th, 25th, 50th, 75th and 97.5th percentiles. The presence or absence of diabetes and other endocrine disorders was also summarized according to the prepregnancy BMI. Descriptive analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS statistics 25.0 (IBM, Chicago, IL, USA) 10.

RESULTS
The present study contained 80,636 pregnant women, including 4,611 women with diabetes, dyslipidemia or endocrine disorders, while excluding women with missing data. A summary of the 80,636 participants is shown in Figure 1. There were 43 participants with type 1 diabetes only, 78 with type 2 diabetes only, 2,315 with GDM only, 354 with dyslipidemia only and 1,821 with other endocrine disorders. HbA1c was higher in participants with pregestational diabetes or GDM only than in healthy participants. Furthermore, HbA1c was higher than the recommended target of 6.5%1 for glycemic control during pregnancy in 39.5% of those with type 1 diabetes only and 24.3% of those with type 2 diabetes only.

Our evaluation of lipid biomarkers showed that participants with type 1 diabetes had slightly better lipid profiles than healthy participants. Lipid profiles in participants with type 2 diabetes were characterized by higher TG levels and lower HDL-C during the first trimester of pregnancy, and a slight increase in lipid levels between the first and second trimesters. TG levels were higher in participants with GDM than in healthy participants, but no differences in the distribution of cholesterol levels, including HDL-C, were observed between these groups. In participants with dyslipidemia, the distribution of HDL-C was similar to those of healthy participants, whereas TC, LDL-C and TG levels were higher than those of healthy participants.

Participants with higher prepregnancy BMI were more likely to have diabetes or endocrine disorders (Table S1).

DISCUSSION
This is the first report of the metabolic profiles of pregnant women, which was based on big data extracted from questionnaires and blood samples taken during pregnancy, obtained from a nationwide large cohort study across Japan. We report changes in the distribution of metabolic biomarkers with the progression of pregnancy, and differences in the distribution of those biomarkers between healthy pregnant women and pregnant women with diabetes or other metabolic disorders.

According to previous reports, HbA1c levels decrease during the second trimester of pregnancy and increase during the third trimester11,12. The participants in the present study also showed a decrease in HbA1c between the first and second trimesters.

HbA1c was higher in participants with pregestational diabetes (type 1 diabetes or type 2 diabetes) or GDM than in healthy participants. Approximately half of the participants had HbA1c levels that were less than the recommended target of 6.5% for glycemic control during pregnancy13, whereas >5.0% had HbA1c levels that were higher than the generally
recommended target of 7.0% as an indicator of glycemic control in the Japanese population\textsuperscript{14}. This observation led us to speculate that our participants often conceived without planning and while their glycemic control was poor.

It is known that levels of cholesterol and TG increase during pregnancy\textsuperscript{2}, and this study also showed that levels of all lipid biomarkers, including HDL-C, across all percentiles, increased as pregnancy progressed. However, the present results also showed that the second-highest TG level was found in the youngest age group (<20 years). This finding is inconsistent with another study that reported that TG levels were significantly higher in women of older ages\textsuperscript{3}. Although the reason for the incongruent results between the present study and the previous study is uncertain, the fact remains that teenage pregnancy carries heightened risks for the mother and newborn. Despite the limitation that blood samples were not obtained after fasting, and were taken at any time, such samples should be informative, because the European Atherosclerosis Society recently recognized that it is not essential to use fasting blood samples to measure lipid profiles\textsuperscript{15}. In addition, our sample size was sufficient to permit accurate statistical analysis.

Figure 1 | Flow chart characterizing the study participants and reasons for their exclusion. GDM, gestational diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.
**Table 1** | Biomarkers classified by percentile in healthy pregnant participants according to body mass index before pregnancy and maternal age

| BMI before pregnancy | n | Adjusted HbA1c (%) | Total cholesterol (mg/dL) | LDL cholesterol (mg/dL) | HDL cholesterol (mg/dL) | Triglyceride (mg/dL) |
|---------------------|---|-------------------|--------------------------|------------------------|------------------------|---------------------|
|                     |   | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th |
| <18.5               |   | 12,148 46 50 51 5.4 5.7 | 137 171 191 216 271 | 58 83 99 118 166 | 5.4 69 78 87 107 | 54 87 112 144 238 |
| 18.5–24             |   | 56,156 46 50 51 5.4 5.7 | 140 175 196 220 273 | 61 88 104 123 168 | 5.2 68 76 86 106 | 56 92 118 154 263 |
| 25–29               |   | 5817 47 51 52 5.5 5.8 | 148 182 204 226 278 | 68 97 114 132 178 | 4.8 63 72 81 100 | 65 109 143 185 326 |
| ≥30                 |   | 1634 48 51 52 5.6 6.0 | 148 185 205 228 280 | 70 102 119 136 180 | 4.6 60 69 77 97 | 72 118 151 197 352 |

Maternal age at registration (years)

| Maternal age at registration (years) | n | Adjusted HbA1c (%) | Total cholesterol (mg/dL) | LDL cholesterol (mg/dL) | HDL cholesterol (mg/dL) | Triglyceride (mg/dL) |
|-------------------------------------|---|-------------------|--------------------------|------------------------|------------------------|---------------------|
|                                    |   | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th |
| <20                                |   | 786 45 48 50 5.2 5.5 | 139 175 194 217 266 | 66 92 108 126 168 | 4.8 64 72 80 102 | 62 97 127 166 293 |
| 21–24                              |   | 7,590 46 49 51 5.2 5.6 | 136 171 193 216 270 | 60 86 103 122 169 | 5.1 66 75 84 104 | 54 90 117 153 258 |
| 25–29                              |   | 22,680 47 50 51 5.3 5.6 | 140 173 194 217 271 | 61 87 103 122 167 | 5.2 67 76 85 105 | 55 89 115 150 260 |
| 30–34                              |   | 20,771 47 50 51 5.2 5.7 | 141 175 197 221 274 | 61 88 104 124 170 | 5.2 68 76 86 106 | 57 93 119 156 270 |
| 35–39                              |   | 15,607 47 51 52 5.4 5.8 | 142 178 199 224 276 | 61 90 106 126 171 | 5.2 68 77 86 107 | 59 96 124 162 276 |
| ≥40                                |   | 2,591 47 51 53 5.5 5.8 | 145 182 203 227 283 | 66 93 110 128 175 | 5.2 68 76 86 106 | 60 100 129 168 288 |

*Adjusted glycated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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**Table 2** | Biomarkers classified by percentile in healthy participants according to the week of pregnancy

| Weeks of pregnancy | n | Adjusted HbA1c (%) | Total cholesterol (mg/dL) | LDL cholesterol (mg/dL) | HDL cholesterol (mg/dL) | Triglyceride (mg/dL) |
|--------------------|---|-------------------|--------------------------|------------------------|------------------------|---------------------|
|                    |   | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th | 2.5th 25th 50th 75th 97.5th |
| First trimester of pregnancy |   |                     |                          |                        |                        |                    |
| 4–7 weeks           |   | 897 47 50 52 5.4 5.7 | 127 162 182 202 249 | 54 80 95 112 154 | 48 63 72 82 101 | 49 80 106 146 255 |
| 8–11 weeks          |   | 16,660 47 50 52 5.4 5.7 | 135 167 186 209 260 | 57 83 98 116 157 | 50 66 74 83 103 | 52 84 109 144 248 |
| 12–13 weeks         |   | 14,75 47 50 52 5.4 5.7 | 137 171 190 212 262 | 59 85 100 118 160 | 51 66 75 84 104 | 55 88 113 147 258 |
| Second trimester of pregnancy |   |                     |                          |                        |                        |                    |
| 14–15 weeks         |   | 13,067 47 50 52 5.4 5.7 | 142 175 196 218 269 | 62 88 104 123 166 | 52 67 76 85 105 | 58 93 119 154 263 |
| 16–19 weeks         |   | 19,726 47 50 51 5.4 5.7 | 147 182 203 227 278 | 65 93 109 128 173 | 53 69 78 87 108 | 62 98 126 162 275 |
| 20–23 weeks         |   | 7,883 46 49 51 5.5 5.7 | 149 189 211 235 268 | 67 97 115 135 181 | 54 70 79 89 108 | 64 103 133 171 294 |
| 24–27 weeks         |   | 26,78 46 49 51 5.3 5.7 | 147 188 211 239 293 | 67 96 115 138 192 | 53 70 79 88 110 | 61 103 133 176 314 |
| Overall             |   | 76,025 47 50 52 5.4 5.7 | 135 168 188 210 261 | 58 84 99 117 158 | 51 66 74 83 103 | 53 86 111 146 253 |

*Adjusted glycated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25. HDL, high-density lipoprotein; LDL, low-density lipoprotein.
### Table 3 | Distribution of biomarkers in pregnant participants with or without diabetes/endocrine disorders

| Variables          | Healthy participants | Participants with type 1 diabetes only | Participants with type 2 diabetes only | Participants with gestational diabetes only | Participants with dyslipidemia only |
|--------------------|----------------------|----------------------------------------|----------------------------------------|--------------------------------------------|-----------------------------------|
|                    | n = 32,136 (1st), 43,899 (2nd) | n = 28 (1st), 15 (2nd) | n = 35 (1st), 43 (2nd) | n = 1,002 (1st), 1,313 (2nd) | n = 149 (1st), 205 (2nd) |
|                    | 25th | 50th | 75th | 97.5th | 2.5th | 25th | 50th | 75th | 97.5th | 2.5th | 25th | 50th | 75th | 97.5th | 2.5th | 25th | 50th | 75th | 97.5th |
| Adjusted HbA1c* (%) | First | 4.7  | 5.0 | 5.2 | 5.4 | 5.7 | 5.2 | 5.9 | 6.0 | 6.7 | 7.0 | 9.1 | 4.8 | 5.2 | 5.4 | 5.6 | 5.9 | 6.4 | 4.7 | 5.1 | 5.2 | 5.5 | 5.9 |
|                    | Second | 4.6 | 5.0 | 5.1 | 5.4 | 5.7 | 5.2 | 5.6 | 6.1 | 6.7 | 7.7 | 4.8 | 5.4 | 6.0 | 6.4 | 7.6 | 4.7 | 5.1 | 5.4 | 5.6 | 6.2 | 4.6 | 5.1 | 5.2 | 5.5 | 5.8 |
| TC (mg/dL) First | 135 | 168 | 188 | 210 | 261 | 122 | 170 | 183 | 210 | 257 | 142 | 166 | 184 | 202 | 234 | 145 | 174 | 195 | 217 | 263 | 158 | 204 | 225 | 251 | 328 |
|                    | Second | 145 | 181 | 203 | 227 | 279 | 142 | 172 | 191 | 214 | 231 | 149 | 182 | 198 | 223 | 289 | 148 | 184 | 206 | 230 | 289 | 158 | 204 | 225 | 251 | 328 |
| LDL-C (mg/dL) First | 58 | 84 | 117 | 158 | 80 | 50 | 75 | 103 | 104 | 132 | 65 | 89 | 124 | 174 | 183 | 64 | 89 | 107 | 124 | 166 | 83 | 113 | 124 | 156 | 232 |
|                    | Second | 64 | 92 | 109 | 128 | 148 | 68 | 90 | 111 | 117 | 148 | 57 | 95 | 105 | 128 | 186 | 66 | 96 | 112 | 132 | 232 | 79 | 126 | 144 | 174 | 261 |
| HDL-C (mg/dL) First | 51 | 66 | 74 | 83 | 103 | 56 | 68 | 78 | 99 | 123 | 33 | 57 | 64 | 73 | 107 | 49 | 63 | 75 | 83 | 101 | 48 | 65 | 75 | 84 | 108 |
|                    | Second | 53 | 69 | 77 | 87 | 107 | 48 | 68 | 72 | 84 | 102 | 43 | 59 | 66 | 81 | 91 | 50 | 66 | 75 | 85 | 104 | 52 | 71 | 80 | 91 | 116 |
| TG (mg/dL) First | 53 | 86 | 111 | 146 | 253 | 45 | 73 | 91 | 126 | 232 | 44 | 112 | 151 | 196 | 255 | 63 | 97 | 127 | 169 | 321 | 64 | 108 | 144 | 200 | 383 |
|                    | Second | 61 | 98 | 125 | 163 | 280 | 46 | 79 | 124 | 180 | 301 | 72 | 123 | 159 | 232 | 434 | 65 | 108 | 142 | 190 | 332 | 72 | 114 | 143 | 195 | 329 |

*Adjusted glycosylated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25.

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.
specific study, and could therefore have resulted in the low prevalence of metabolic disorders overall.

In summary, we have reported the time course of glucose and lipid metabolic biomarkers during pregnancy in Japanese women enrolled in the JECS. The distribution of these biomarkers was affected by the time of blood sample collection, as well as the presence or absence of underlying diseases. Monitoring pregnant women with poor glycemic and lipid profile is crucial to control and optimize these levels in reducing the risks of adverse pregnancy outcomes. In the future, the JECS will elucidate the influences of metabolic status during pregnancy on the health and development of the children born during the study.

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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Distribution of participants with or without diabetes/endocrine disorders by body mass index before pregnancy