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ARTICLE

Association between alcohol consumption during pregnancy and hypertensive disorders of pregnancy in Japan: the Japan Environment and Children's Study

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Abstract

This study examined the association between maternal alcohol consumption during pregnancy and hypertensive disorders of pregnancy in the Japan Environment and Children's Study, a nationwide birth cohort study. A total of 76 940 pregnant women were included in the analysis. Information about alcohol consumption during pregnancy was obtained using two questionnaires: T1 and T2. The mean (standard deviation) gestational age in the T1 and T2 questionnaires were 16.5 (5.8) and 27.9 (3.7) weeks, respectively. Alcohol consumption was considered as an exposure, hypertensive disorders of pregnancy as an outcome, and possible confounding factors were included in a generalized linear mixed-effects model with a logit link function. Among the study subjects, 2 348 (3.1%) women developed hypertensive disorders of pregnancy. Compared with 25 300 women who never drank alcohol, 43 women who drank alcohol according to the T1 questionnaire and continued to drink ≥150 g ethanol/week according to the T2 questionnaire had significantly higher odds of hypertensive disorders of pregnancy. The adjusted odds ratio was 3.98 (95% confidence interval [CI], 1.33–11.9). In conclusion, alcohol consumption of ≥150 g ethanol/week during pregnancy is better avoided because of the high odds of developing hypertensive disorders of pregnancy. It may be meaningful that healthcare providers confirm information about alcohol consumption during pregnancy. Moreover, discontinuation of alcohol consumption is recommended to prevent the onset of hypertensive disorders of pregnancy in Japan.

Keywords Alcohol · Hypertensive disorders of pregnancy · Pregnancy

Introduction

Maternal alcohol consumption during pregnancy is speculated to be related to adverse perinatal outcomes. Heavy

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drinking can lead to fetal alcohol syndrome, low birth weight, preterm birth, small for gestational age births, and adverse effects on the child's neurodevelopment. [1, 2] In addition, hypertensive disorders of pregnancy (HDP), a group of common maternal complications during pregnancy, are also associated with adverse perinatal outcomes. [3] HDP include chronic hypertension, preeclampsia, gestational hypertension, preeclampsia superimposed on chronic hypertension, and eclampsia. Although angiogenic imbalance is one of the etiologies of HDP, a definitive etiology is unknown. [4] Several factors, such as obesity, nulliparity, multiple pregnancy, and gestational diabetes mellitus, are known risk factors for HDP. [3]

Maternal lifestyle habits, such as alcohol consumption, may be related to HDP. However, the conclusions of previous studies about the association between alcohol consumption and HDP are inconsistent. Several studies have reported that women who consume alcohol during pregnancy have lower odds of preeclampsia. [5–7] By contrast, another study reported that these women have higher odds of HDP. [8] Other studies have shown that alcohol consumption during pregnancy is not significantly associated with preeclampsia. [9, 10] Therefore, this study was performed to evaluate the association between alcohol consumption during pregnancy and HDP.

Methods

Study design and participants

This study was part of the Japan Environment and Children's Study (JECS), a nationwide birth cohort study conducted in Japan. JECS primarily aims to evaluate the association between environmental factors and children's health and development. Pregnant women were recruited from 15 regional centers (Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and south Kyusyu/Okinawa) between January 2011 and March 2014. Written informed consent was obtained from all participants. The JECS protocol was approved by the Institutional Review Board of the Ministry of Environment and all participating institutions. Details about the study design of JECS were previously described. [11–14] We analyzed the data sets "jecs-ag-20160424" and "allbirth_revice001_ver001," which were released by the national center in June 2016 and October 2016, respectively. The data set contains 103 099 subjects. In JECS, study subjects answered two questionnaires during pregnancy. The first and second questionnaires were the T1 questionnaire and the T2 questionnaire, respectively. [12]

Data collection

Alcohol consumption during pregnancy

Information about alcohol consumption during pregnancy, the exposure in this study, was obtained from the two questionnaires, namely, T1 and T2. In the T1 questionnaire, study subjects answered from the following choices: "Never," "Quit drinking," and "Continue drinking during pregnancy." In this questionnaire, the amount of alcohol consumption as ethanol (g/week) during pregnancy was not evaluated. In the T2 questionnaire, subjects also answered from the following choices: "Never," "Quit drinking before conception was recognized," "Quit drinking after conception was recognized," and "Continue drinking during pregnancy." If subjects answered "Continue drinking during pregnancy," ethanol (g/week) as alcohol consumption during pregnancy was evaluated using the food frequency questionnaires used in the Japan Public Health Center-based Prospective Study for the Next Generation. [12, 15] JECS provided the amount of ethanol (g/week) in the data set "jecs-ag-20160424." Subjects who answered "Almost no drinking" among those who answered "Continue drinking during pregnancy" in the T2 questionnaire were classified into their own category.

Thus far, a meaningful cutoff value for ethanol consumption (g/week) during pregnancy based on perinatal outcomes has not been determined. Therefore, we first used the following categories: <150 g ethanol/week, 150–299 g ethanol/week, and ≥300 g ethanol/week, which were used in the Japan Public Health Center-based Prospective Study. [16] However, the highest category of alcohol consumption in the T2 questionnaire was defined as ≥150 g ethanol/week in this study because the number of subjects with ≥300 g ethanol/week was small.

Based on the T1 questionnaire only, the subjects in this study were divided into three categories as follows: "Never," "Quit drinking," and "Drinking." Based on the T2 questionnaire only, subjects were also divided into four categories as follows: "Never," "Quit drinking before conception was recognized," "Quit drinking after conception was recognized," and "Drinking." Furthermore, subjects with "Drinking" were subdivided into "Almost no drinking," "<150 g ethanol/week," and "≥150 g ethanol/week."

In addition, subjects were classified based on both the T1 and T2 questionnaires. Subjects who answered "Never" or "Quit drinking" in T1 and "Continue during pregnancy" in T2 were combined in each category of the T2 questionnaire (i.e., "Almost no drinking," "<150 g ethanol/week," and "≥150 g ethanol/week") because of the small sample size. Finally, subjects were classified into 10 categories based on information regarding alcohol consumption from both the T1 and T2 questionnaires.

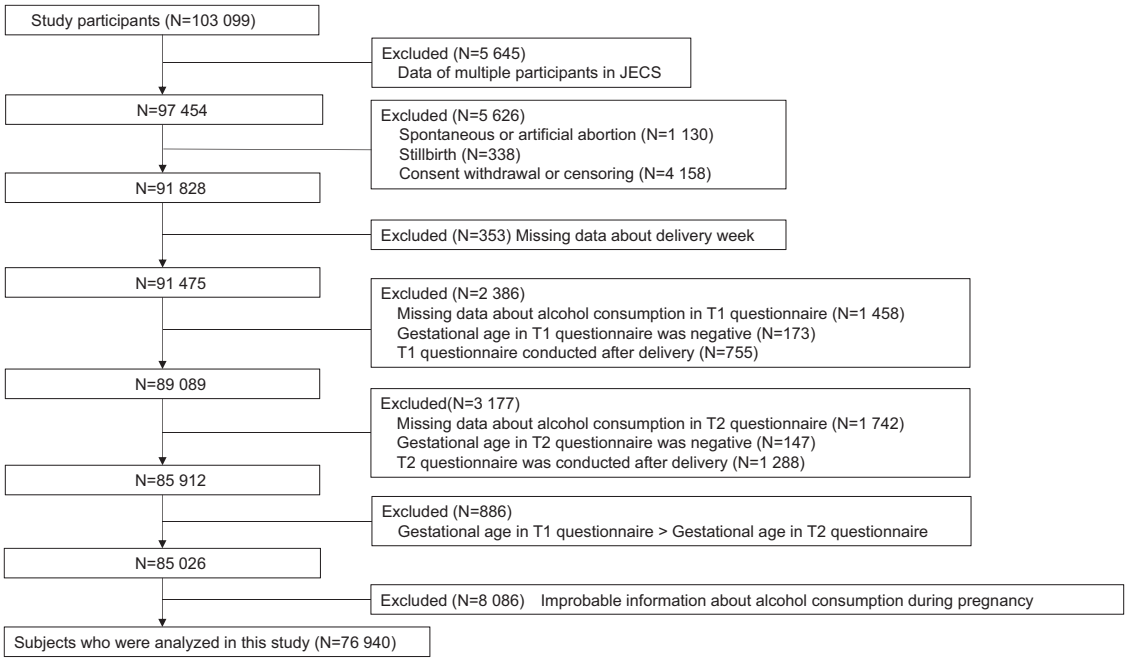

Fig. 1 Flow chart of study inclusion

Diagnosis of hypertensive disorders of pregnancy

The outcome in this study is HDP. HDPs are diagnosed when systolic blood pressure (SBP) is ≥140 mmHg and/or diastolic blood pressure (DBP) is ≥90 mmHg after 20 weeks of gestation in pregnant women without a past history of hypertension and when proteinuria (≥300 mg/24 h) occurs after 20 weeks of gestation in pregnant women with a past history of hypertension. The severity of HDP is classified by both blood pressure and proteinuria. Mild HDP is diagnosed when SBP is ≥140 mmHg and/or DBP is ≥90 mmHg but SBP is <160 mmHg and DBP is <110 mmHg after 20 weeks of gestation and proteinuria is ≥300 mg/24 h without exceeding 2.0 g/24 h or 3 + dipstick. Severe HDP is diagnosed when SBP is ≥ 160 mmHg and/or DBP is ≥110 mmHg and proteinuria exceeds 2.0 g/24 h or 3 + dipstick. [17] These criteria are based on the Japanese Society for the Study of Hypertension in Pregnancy guidelines. [17] Information about HDP was obtained from medical records.

Other variables used in this study

Regional centers where the subjects belonged, maternal age in questionnaire T1, method of conception, parity, multiple pregnancy, smoking status, maternal education, annual income, marital status, folate supplementation, psychological stress, year of delivery, prepregnancy height and body weight (BW), BW at delivery, and gestational age in both T1 and T2 questionnaires were collected. Past history of perinatal outcomes, including spontaneous abortion, placental abruption, and HDP, was also collected. Obstetrical complications, including placenta previa and gestational diabetes mellitus during the current pregnancy, were obtained. Maternal age in the T1 questionnaire was classified as follows: <25 years, 25–29.9 years, 30–34.9 years, 35–39.9 years, and ≥40 years. The prepregnancy body mass index (BMI) was calculated as prepregnancy BW in kilograms/(height in meters)^2. Subjects were classified according to WHO BMI cutoff points: underweight (<18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). [18] Gestational weight gain (GWG) was calculated by subtracting prepregnancy body weight from body weight at the time of delivery. GWG was classified as follows: <7, 7–11.9, and ≥12 kg. The method of conception was classified into spontaneous pregnancy, non-assisted reproductive technology, including ovulatory induction and artificial insemination by the husband, and assisted reproductive technology. Marital status was defined as follows: married, unmarried, divorced, or widowed. Maternal education was classified into junior high school, high school, technical college, special school, junior college, university, and graduate school. Annual income was categorized into <2, 2–3.99, 4–5.99, 6–7.99, 8–9.99, 10–11.99, 12–14.99, 15–19.99, and ≥20 million Japanese yen. Information about smoking status, folate supplementation, and psychological stress was obtained from both the T1 and T2 questionnaires. Psychological stress was defined as Kessler psychological distress scale (K6) ≥ 13, based on a previous report. [19, 20] Information about past history of hypertension, diabetes mellitus (type 1 or type 2), hyperthyroidism, hypothyroidism, mental illness, renal

disease and systemic lupus erythematosus, and antiphospholipid syndrome was also obtained. Subjects with depression, anxiety disorder, schizophrenia, or dysautonomia were defined as women with a past history of mental illness. Renal disease was defined as IgA nephropathy and/or nephrotic syndrome in this study.

Statistical analysis

To examine the association between alcohol consumption during pregnancy and HDP, we applied a generalized linear mixed-effects model with a logit link function. [21] The categories of alcohol consumption during pregnancy and possible confounding factors were included in the model. The categories of alcohol consumption in the T1 or T2 questionnaire only were initially included in the model as an exposure. Subsequently, these categories, based on both the T1 and T2 questionnaires, were included in the model as an exposure. Details of the statistical analyses are described in the Supplementary information.

Results

Maternal characteristics of study participants

Figure 1 shows the study inclusion flow chart. Among the 103 099 study participants in the data sets "jecs-ag-20160424" and "allbirth_revice001_ver001," only the initial participation data were used for the 5 645 women who participated multiple times in JECS. Spontaneous or artificial abortion (1 130 women), stillbirth (338 women), consent withdrawal or censoring (4 158 women), missing data about alcohol consumption during pregnancy in the T1 questionnaire (1 458 women), improbable value (i.e., negative value) for gestational age in the T1 questionnaire (173 women), and cases where the T1 questionnaire was conducted after delivery (755 women) were excluded. Women with missing data about alcohol consumption during pregnancy in the T2 questionnaire (1 742 women), improbable value (i.e., negative value) for gestational age in the T2 questionnaire (147 women), and T2 questionnaires conducted after delivery (1 288 women) were also excluded. In addition, 886 women whose gestational age in the T1 questionnaire was later than that in the T2 questionnaire were excluded.

A total of 8 086 women who had improbable information about alcohol consumption were excluded. Details about improbable information about alcohol consumption during pregnancy are described in the Supplementary information. Finally, 76 940 women were analyzed in this study.

Table 1 shows maternal characteristics of the study subjects. The mean (standard deviation) gestational ages in

Table 1 Maternal characteristics of study participants

Characteristics	Study participants
Number of subjects	76 940
Gestational age in the T1 questionnaire (weeks)	16.5 (5.8)
Gestational age in the T2 questionnaire (weeks)	27.9 (3.7)
Alcohol consumption during pregnancy	
T1 questionnaire (%)	
Never	33.0
Used to drink	57.5
Drinking	9.5
T2 questionnaire (%)	
Never	32.9
Quit drinking before pregnancy was confirmed	15.0
Quit drinking after pregnancy was confirmed	49.5
Drinking	2.6
Almost no drinking	0.8
<150 g ethanol/week	1.7
Ethanol (g/week, median, IQR)	9.0, 5.8–24.0
≥150 g ethanol/week	0.1
Ethanol (g/week, median, IQR)	245.1, 166.3–379.5
Age in the T1 questionnaire (%)	
<25 years	10.8
25–29.9 years	29.1
30–34.9 years	35.3
35–39.9 years	21.2
≥40 years	3.7
Pre-pregnancy BMI (%)	
<18.5 kg/m^2, underweight	17.2
18.5–24.9 kg/m^2, normal range	72.0
25.0–29.9 kg/m^2, overweight	7.2
≥30 kg/m^2, obese	2.2
Missing	1.5
Gestational weight gain (%)	
<7 kg	15.0
7–11.9 kg	48.0
≥12 kg	33.6
Missing	3.4
Parity (%)	
Primipara	42.0
Multipara	55.6
Missing	2.4
Marital status (%)	
Married	95.2
Unmarried	3.5
Divorced or widowed	0.9
Missing	0.4

Table 1 (continued)

Characteristics	Study participants
Conception method (%)	
Spontaneous pregnancy	92.6
Non-ART	3.8
ART	3.2
Missing	0.4
Multiple pregnancy (%)	0.9
Annual income (million, Japanese Yen, %)	
<2	5.2
2–3.99	32.0
4–5.99	30.9
6–7.99	15.0
8–9.99	6.2
10–11.99	2.3
12–14.99	0.9
15–19.99	0.5
≥20	0.3
Missing	6.8
Final education (%)	
Junior high school	4.6
High school	30.9
Technical college	1.6
Special school	22.9
Junior college	17.7
University	20.5
Graduate school	1.5
Missing	0.4
Smoking status (%)	
Never	56.4
Ever	33.8
Continue smoking during pregnancy	4.3
Missing	5.5
Past-history of spontaneous abortion (%)	
Yes	20.9
No	56.0
Missing	23.1
Past-history (%)	
Placental abruption	0.3
Hypertension	0.5
HDP	1.8
Type 1 diabetes mellitus	0.1
Type 2 diabetes mellitus	0.1
Hyperthyroidism	1.1
Hypothyroidism	1.0
Kidney disorder	0.4
SLE	0.1
Mental illness	7.8
APS[a]	0.2
K6 (%)[b]	
<13 in both T1 and T2 questionnaires	92.9
≥13 in only the T1 questionnaire	2.2
≥13 in only the T2 questionnaire	2.0
≥13 in both T1 and T2 questionnaires	1.1
Missing	1.8
Intake of folate supplement (%)	
Neither in the T1 nor T2 questionnaires	42.8
Yes, in only the T1 questionnaire	13.6
Yes, in only the T2 questionnaire	7.0
Yes, in both T1 and T2 questionnaires	36.1
Missing	0.5
Obstetric complications	
HDP (%)	3.1
Severity	
Mild HDP	2.1
Severe HDP	0.9
Missing	0.1
GDM (%)	2.7
Placenta previa (%)	0.6
Preterm delivery (%)[c]	4.7
Year of delivery (%)	
2011	10.2
2012	29.8
2013	35.5
2014	24.5
Gestational age at delivery (week)	39.3 (1.5)
Placental weight in singleton births (g)[d]	560 (116)

Data are shown as mean (standard deviation) or percentages

APS antiphospholipid syndrome, *ART* assisted reproductive technology, *BMI* body mass index, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *IQR* interquartile range, *SLE* systemic lupus erythematosus

[a]Eleven subjects (0.01%) had missing data of APS

[b]Kessler psychological distress scale

[c]Preterm delivery was defined as delivery before 36 weeks gestation

[d]2 762 subjects had missing data of placental weight

the T1 and T2 questionnaires were 16.5 (5.8) and 27.9 (3.7) weeks, respectively. Only 58 (0.1%) women consumed ≥ 150 g ethanol/week according to the T2 questionnaire in this study, and 2 348 (3.1%) women developed HDP. Supplementary Tables 1 and 2 show differences in maternal characteristics based on categories of alcohol consumption during pregnancy in the T1 and T2 questionnaires, respectively.

Table 2 Association between alcohol consumption in the T1 questionnaire and HDP

Alcohol consumption in the T1 questionnaire	*n*	HDP *n* (%)	Crude OR (95% CI) [b]	Adjusted OR (95% CI) [a,b]
Never	25 364	811 (3.2)	Reference	Reference
Used to drink	44 253	1 316 (3.0)	0.93 (0.85-1.02)	0.90 (0.82–0.99)
Drinking	7 323	221 (3.0)	0.93 (0.80-1.09)	0.96 (0.82–1.13)

APS antiphospholipid syndrome, *BMI* body mass index, *CI* confidence interval, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *OR* odds ratio, *SLE* systemic lupus erythematosus

[a]Adjusted by maternal age in the T1 questionnaire, pre-pregnancy BMI, gestational weight gain, parity, past history of spontaneous abortion, past history of placental abruption, multiple pregnancy, previa, GDM, smoking status, maternal education, income, marital status, folate supplementation, Kessler psychological distress scale (K6), year of delivery, past histories of diseases (hypertension, HDP, type 1 diabetes mellitus, type 2 diabetes mellitus, hyperthyroidism, hypothyroidism, kidney disorder, SLE, APS, and mental illness), and gestational age in T1 and T2 questionnaires

[b]Twenty clusters, regional centers and subunits were included into the model as random intercepts

Table 3 Association between alcohol consumption in the T2 questionnaire and HDP

Alcohol consumption in the T2 questionnaire	*n*	HDP *n* (%)	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[a,b]
Never	25 300	809 (3.2)	Reference	Reference
Quit drinking before pregnancy was confirmed	11 568	334 (2.9)	0.91 (0.79-1.03)	0.89 (0.78-1.02)
Quit drinking after pregnancy was confirmed	38 107	1 152 (3.0)	0.94 (0.86–1.03)	0.92 (0.83–1.01)
Drinking				
Almost no drinking	610	16 (2.6)	0.80 (0.48–1.34)	0.93 (0.56–1.56)
<150 g ethanol/week	1 297	32 (2.5)	0.75 (0.52–1.08)	0.83 (0.57–1.21)
≥150 g ethanol/week	58	5 (8.6)	2.74 (1.08–6.98)	3.45 (1.32–9.05)

APS antiphospholipid syndrome, *BMI* body mass index, *CI* confidence interval, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *OR* odds ratio, *SLE* systemic lupus erythematosus

[a]Adjusted by maternal age in the T1 questionnaire, pre-pregnancy BMI, gestational weight gain, parity, past history of spontaneous abortion, past history of placental abruption, multiple pregnancy, previa, GDM, smoking status, maternal education, income, marital status, folate supplementation, Kessler psychological distress scale (K6), year of delivery, past histories of diseases (hypertension, HDP, type 1 diabetes mellitus, type 2 diabetes mellitus, hyperthyroidism, hypothyroidism, kidney disorder, SLE, APS, and mental illness), and gestational age in T1 and T2 questionnaires

[b]Twenty clusters, regional centers and subunits were included into the model as random intercepts

Association between alcohol consumption in the T1 questionnaire and HDP (Table 2)

Table 2 shows the association between alcohol consumption in the T1 questionnaire and HDP. Compared with subjects who had never drank alcohol, subjects who used to drink alcohol had significantly lower odds of HDP (adjusted odds ratio [OR], 0.90; 95% confidence interval [CI], 0.82–0.99).

Association between alcohol consumption in the T2 questionnaire and HDP (Table 3)

Table 3 shows the association between alcohol consumption in the T2 questionnaire and HDP. Subjects who consumed ≥150 g ethanol/week had significantly higher odds of HDP compared with those who had never consumed alcohol (adjusted OR, 3.45; 95% CI, 1.32–9.05).

Association between alcohol consumption based on both T1 and T2 questionnaires and HDP (Table 4)

Table 4 shows the association between alcohol consumption during pregnancy and HDP after the T1 and T2 questionnaires were combined. Among the 43 subjects who drank according to the T1 questionnaire and consumed ≥150 g ethanol/week according to the T2 questionnaire, four developed HDP. These women had significantly higher odds of HDP compared to those who had never consumed alcohol in both the T1 and T2 questionnaires. The adjusted OR was 3.98 (95% CI, 1.33–11.9). Among the 31 921 subjects who used to drink alcohol according to the T1 questionnaire and quit drinking after pregnancy was confirmed, according to the T2 questionnaire, 958 developed HDP. These women had significantly lower odds of HDP compared with those who had

Table 4 Association between alcohol consumption based on both T1 and T2 questionnaires and HDP[a,b]

T2 questionnaire / T1 questionnaire	Never	Quit drinking before pregnancy was confirmed	Quit drinking after pregnancy was confirmed	Drinking		
				Almost no drinking	<150 g ethanol/ week	≥150 g ethanol/ week
Never	809/25 300 3.2% Reference	–	–	9/279 3.2% 1.08 (0.54–2.16)	16/534 3.0% 1.09 (0.65–1.82)	1/15 6.7% 2.28 (0.29–17.8)
Used to drink	–	334/11 568 2.9% 0.89 (0.78–1.02)[c]	958/31 921 3.0% 0.90 (0.82–0.99)[d]			
Drinking	–	–	194/6 186 3.1% 0.99 (0.84–1.17)[e]	7/331 2.1% 0.80 (0.37–1.72)	16/763 2.1% 0.67 (0.40–1.13)	4/43 9.3% 3.98 (1.33–11.9)

Data are shown as follows: number of HDP/ number of subjects, percentage of HDP, and adjusted ORs (95% CI)

APS antiphospholipid syndrome, *BMI* body mass index, *CI* confidence interval, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *OR* odds ratio, *SLE* systemic lupus erythematosus

[a]Adjusted by maternal age in the T1 questionnaire, pre-pregnancy BMI, gestational weight gain, parity, past history of spontaneous abortion, past history of placental abruption, multiple pregnancy, previa, GDM, smoking status, maternal education, income, marital status, folate supplementation, Kessler psychological distress scale (K6), year of delivery, past histories of diseases (hypertension, HDP, type 1 diabetes mellitus, type 2 diabetes mellitus, hyperthyroidism, hypothyroidism, kidney disorder, SLE, APS, and mental illness), and gestational age in T1 and T2 questionnaires

[b]Twenty clusters, regional centers and subunits were included into the model as random intercepts

[c]This category indicates that "Quit drinking before pregnancy was confirmed"

[d]This category indicates that "Quit drinking before T1 questionnaire"

[e]This category indicates that "Quit drinking after T1 questionnaire"

never consumed alcohol in both the T1 and T2 questionnaires. The adjusted OR was 0.90 (95% CI, 0.82–0.99). Other categories of alcohol consumption during pregnancy were not significantly associated with HDP.

Discussion

To our knowledge, this study is the first to show the association between alcohol consumption during pregnancy and HDP in Japan. Alcohol consumption of ≥150 g ethanol/ week throughout pregnancy was a risk factor for HDP in Japan. In addition, the discontinuation of alcohol consumption before or during pregnancy seemed to not increase the odds of HDP. Decreased point estimates of the ORs of HDP were noted among women who quit drinking alcohol before or during pregnancy compared to women who had never consumed alcohol. Selection bias and reverse causality might have occurred in observational studies, as recently reported. [22] Alcohol consumption is a possible modifiable health factor. [3] Therefore, alcohol consumption is better avoided in women who desire to bear children. In addition, abstaining from alcohol consumption after conception is beneficial to prevent the increased possibility of HDP. For healthcare providers, our results may also present the importance of addressing alcohol consumption at prenatal checkups, considering the HDP in Japan.

In this study, the adjusted ORs of HDP for women who continued to drink alcohol, according to the T2 questionnaire, excluding the 43 subjects who drank alcohol according to the T1 questionnaire and drank ≥150 g ethanol/ week according to the T2 questionnaire, were not statistically significant (Table 4). This finding does not indicate safety in perinatal care, because alcohol consumption during pregnancy has adverse effects on the child's neurodevelopment, as reported in previous studies. [23]

Our results were similar to those of Ye et al. who reported that alcohol consumption results in significantly high odds of HDP in China, but the amount of alcohol was unclear. [8] However, our results were not consistent with those of several studies. [5–7] Previous studies have reported a negative association between alcohol consumption during pregnancy and preeclampsia. This difference may be attributed to several reasons. First, gestational hypertension was not considered as an outcome in previous studies. [5–7] The HDP in the current study included both preeclampsia and gestational hypertension, whereas the

HDP in previous studies focused on preeclampsia as an outcome. Second, ethnic differences in the association between alcohol consumption and HDP may be present. For example, Chang et al. reported that the association between smoking during pregnancy and HDP is varied by maternal race and ethnicity. [24] Their study indicated the possibility of racial differences in the association between maternal exposure during pregnancy and HDP.

The definitive mechanism of HDP development induced by alcohol is unclear. Maternal endothelial dysfunction due to several mechanisms contributes to the onset of HDP, particularly preeclampsia. [25, 26] Insufficient spiral artery remodeling results in inadequate placental perfusion and an imbalance of endogenous angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF). [25, 26] An angiogenic imbalance leads to endothelial dysfunction and development of clinical symptoms, such as hypertension, proteinuria, and intrauterine growth restriction. Gundogan et al. reported that alcohol exposure during pregnancy results in maladaptation of uterine spiral artery remodeling in rats. [27] Naik et al. also reported that alcohol exposure during pregnancy induces constriction of the uterine artery in rats. [28] Based on their findings, we speculate that insufficient spiral artery remodeling induced by alcohol exposure during pregnancy following an angiogenic imbalance led to our results. We could not evaluate the association between alcohol consumption and angiogenic imbalance because sFlt-1 and PlGF are not measured in this study. Therefore, further studies are needed to examine this issue.

The strengths of this study are as follows. First, many variables, including maternal characteristics, lifestyle, and socioeconomic factors, were obtained and considered in the statistical analyses. Second, this was a nationwide prospective birth cohort study and comprised a large number of participants. Therefore, the external validity for the Japanese population is high. In fact, maternal characteristics, such as the proportion of primiparous subjects and maternal age ≥ 35 years, were similar to those of vital statistics in Japan. [29] In addition, the proportion of primiparous subjects, maternal age ≥ 35 years, prepregnancy BMI ≥ 25 kg/m^2, and HDP were similar to those in a previous study conducted in Japan. [30] However, whether the findings in this study can be extrapolated to other countries is unclear because of the difference in race.

This study has several limitations. First, information regarding the subclassification of HDP, such as preeclampsia and gestational hypertension, was not obtained. Leemaqz et al. reported the association between alcohol consumption during pregnancy and preeclampsia and gestational hypertension. [31] In their study, women who quit drinking alcohol before 15 weeks gestation had lower odds of preeclampsia and had higher odds of gestational hypertension. Among women who continued drinking alcohol at 20 weeks of gestation, the association between alcohol consumption and preeclampsia was not statistically significant. The point estimate of the adjusted ORs of gestational hypertension was high, but was not statistically significant. In this study, differences in the association between alcohol consumption and preeclampsia or gestational hypertension could not be evaluated. However, a previous study showed that both preeclampsia and gestational hypertension are associated with adverse perinatal outcomes. [32] Preeclampsia and gestational hypertension are risk factors for future cardiovascular diseases, such as stroke, heart disease, renal disease, and hypertension. [33] Therefore, discontinuation of alcohol consumption during pregnancy may be meaningful regardless of HDP subclassification (i.e., preeclampsia or gestational hypertension). Subsequently, discontinuation of alcohol consumption during pregnancy may prevent future cardiovascular diseases by not increasing the odds of HDP. Second, an accurate gestational age at which HDPs were diagnosed was not available in this study. Therefore, we could not examine the association between alcohol consumption and early and late-onset HDP. Different pathophysiologies among early and late-onset preeclampsia have been suggested. [34, 35] Therefore, further studies in Japan are necessary based on the gestational age when HDP was diagnosed. Third, details regarding the measuring devices used in each center to measure blood pressure were not collected. We could not determine whether validated devices were used for the measurements. Measurement error might have occurred when blood pressure was evaluated. Fourth, the association between the change in consumption of ethanol during pregnancy and HDP could not be evaluated in this study. To examine this issue, further studies are warranted. In addition, the number of subjects who drank ≥ 150 g ethanol/week was small. Therefore, further studies with a larger sample size are necessary to reproduce the association between alcohol consumption during pregnancy and HDP.

Furthermore, other lifestyle factors might affect the association between alcohol consumption during pregnancy and HDP. Compared with women who have never consumed alcohol, subjects who drank ≥150 g of ethanol/week had low socioeconomic status, as described in Supplementary Table 2. Therefore, among those subjects, not only alcohol consumption but also unmeasured factors associated with low socioeconomic status, such as periodontal disease and infection, which are associated with an unhealthy lifestyle, might increase the odds of HDP in this study. [36–39]

In conclusion, alcohol consumption during pregnancy, in particular ≥150 g ethanol/week, was found to be a risk factor for HDP in Japan. Alcohol consumption ≥150 g ethanol/week during pregnancy is better avoided because of the

high odds of developing HDP. It may be meaningful that healthcare providers confirm information about alcohol consumption during pregnancy. Discontinuation of alcohol consumption is recommended to avoid increasing the odds of HDP in Japan.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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