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Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

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4 1 **Title:** Pre-pregnancy body mass index and other risk factors for early- and late-onset
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7 2 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-
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10 3 based retrospective cohort study.

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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27 24 **Abstract**

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31 25 **Background:** Obesity increases risk of pre-eclampsia, but the association with
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35 26 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
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38 27 understudied.

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42 28 **Objective:** To examine the association between pre-pregnancy body-mass-index (BMI)
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45 29 and HELLP syndrome, including early- vs. late-onset disease.

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48 30 **Study Design:** A retrospective cohort study, population-based data.

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52 31 **Setting:** British Columbia (BC), Canada, 2008/09-2019/20.

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56 32 **Population:** All pregnancies resulting in live births or stillbirths at ≥ 20 weeks' gestation.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Methods: BMI categories (kg/m^2) included: underweight (<18.5), normal (18.5 - 24.9), overweight (25.0 - 29.9), and obese (≥ 30.0). Rates of early- and late-onset HELLP syndrome (<34 vs. ≥ 34 weeks, respectively) were calculated per 1000 ongoing pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to assess the associations between risk factors (BMI and, e.g., maternal age, parity) and early- vs late-onset HELLP syndrome.

Main outcome measures: HELLP syndrome.

Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 per 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI, overweight and obese categories, respectively. Overall, gestational age-specific rates increased with pre-pregnancy BMI. Adjusted hazard ratio [AHR] was 2.24 for early-onset (95% confidence interval [CI] 1.65-3.04) vs. AHR 1.48 (95% CI 1.23-1.80) for late-onset HELLP syndrome (p-value for interaction 0.025), compared with normal BMI as the reference group. Chronic hypertension, multiple gestation, bleeding (<20 weeks'

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 47 gestation and antepartum) also showed differing AHRs between early- vs. late-onset

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9 48 HELLP.

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12 49 **Conclusions:** Pre-pregnancy BMI is positively associated with HELLP syndrome and the

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15 50 association is stronger with early-onset HELLP syndrome. Associations with early- and

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19 51 late-onset HELLP syndrome differed for some risk factors, suggesting possible

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23 52 differences in etiologic mechanisms.

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26 53 **Strengths and limitations of this study**

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29 54 • We were able to describe gestational age-specific incidence of HELLP

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33 55 syndrome, which requires population data on all pregnancies.

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36 56 • Population-based design coupled with detailed information about demographic,

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40 57 behavioural and clinical factors that allowed for robust adjustment for possible

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44 58 confounding.

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47 59 • We did not have detailed information on laboratory values used for the diagnosis

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50 60 of HELLP syndrome and therefore we were not able to estimate the severity of

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54 61 HELLP.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

- 62 • We did not have information about race/ethnicity, socio-economic status (SES)
63 and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- 64 • Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had
65 missing information about BMI, we used multiple imputation methods to address
66 this limitation.

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74 sources were not involved in study design, data collection, analysis, and interpretation,
75 writing of the manuscript, and/or decision to submit the article for publication.

76 Competing interests statement

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 77 The authors report no conflict of interest.

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8 78 **Key words**

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12 79 Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity,
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16 80 pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP
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22 82 **Word count: 3036**

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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97 Introduction

98 Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the
99 leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies
100 worldwide^{1,2} and accounting for up to 14% of maternal deaths.³ Early-onset PE at <34
101 weeks' gestation is often associated with placental insufficiency whereas late-onset PE
102 is often associated with pre-existing maternal health conditions such as metabolic
103 syndrome and obesity.⁴ Early- vs late-onset PE differ in some risk factors, clinical
104 management and rates of adverse perinatal outcomes.^{5,6} Hemolysis, elevated liver
105 enzymes, and low platelets (HELLP) syndrome occurs in 0.2-0.8% of pregnancies⁷⁻⁹
106 and 10-20% of cases of severe PE.¹⁰ Although HELLP syndrome has been

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107 distinguished from PE as a separate disease,¹¹ it is still widely regarded as a form of
108 severe PE.⁹ While the distinction between early- and late-onset PE and the differences
109 in the association with pre-pregnancy obesity has been established, these differences
110 have not been studied in HELLP syndrome.

111 Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.¹²⁻¹⁵ To
112 date, the world prevalence of obesity has nearly tripled since 1975¹⁶ and the proportion
113 of pregnant women with obesity ranges from 1.8% to 25.3% globally.¹⁷ The prevalence
114 of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada¹⁸ and 29.0% in
115 2019 in the United States.¹⁹ Despite the large increases in obesity in high income
116 countries, the association between maternal pre-pregnancy body-mass-index (BMI) and
117 HELLP syndrome has not been adequately assessed in a large population-based study
118 to date.

119 We carried out a population-based, retrospective cohort study to examine the
120 association between maternal pre-pregnancy BMI and HELLP syndrome and to assess
121 differences in this association in early- vs late-onset HELLP syndrome. We

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

122 hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this
123 relationship may be different in early- compared with late-onset disease. In additional
124 analyses, we examined other risk factors for HELLP syndrome in terms of their
125 association with early- vs late-onset HELLP syndrome.

126 **Materials and Methods**

127 *Data sources and study population*

128 The study included all live births and stillbirths at ≥ 20 weeks' gestation in British
129 Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from
130 the British Columbia Perinatal Database Registry (BCPDR).²⁰ The BCPDR includes
131 information on >99% of births in BC, with detailed data on maternal demographic
132 characteristics, prenatal care, pregnancy complications, labor and delivery
133 characteristics and neonatal outcomes. Each record, abstracted from medical charts (or
134 midwives' notes), includes also up to 25 ICD-10-CA (International Classification of
135 Diseases, 10th Edition, Canada) codes for diagnoses related to delivery hospitalization
136 and following hospital transfers if applicable. Chart abstraction is standardized and

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 137 conducted by trained personnel, and data quality is routinely assessed. Prior validation
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8 138 studies showed high accuracy of collected information on labor and delivery.²¹

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13 139 *Pre-pregnancy BMI and HELLP syndrome*

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17 140 Pre-pregnancy weight and height were based on maternal self-report or health care
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20 141 provider assessment at ≤ 11 weeks' gestation.²² Body-mass-index (BMI) was classified
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24 142 as follows (in kg/m²): underweight (< 18.5), normal (18.5-24.9), overweight (25.0-29.9),
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27 143 and obese (≥ 30.0).²³ The primary outcome of this study was a physician diagnosis of
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31 144 HELLP syndrome in the medical chart, abstracted and recorded in the BCPDR. In
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34 145 Canada, HELLP syndrome is typically diagnosed by the following criteria: LDH ≥ 600
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38 146 IU/l, liver transaminases (AST and ALT) elevated more than twice the upper limit of
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41 147 normal, and a platelet count $< 100,000/\mu\text{l}$ ($10^9/\text{l}$). Early- and late-onset HELLP syndrome
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45 148 were defined as HELLP syndrome with delivery at < 34 weeks and ≥ 34 weeks'
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48 149 gestation, respectively. Early pregnancy ultrasound was used to ascertain gestational
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52 150 age, and last menstrual period was used for those with missing early pregnancy
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55 151 ultrasound.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

152 ***Covariates***

153 In addition to BMI, we examined the association between maternal age, nulliparity, pre-
154 existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple
155 gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance
156 use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol
157 use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as
158 potential confounders; all these factors are known to be associated with HELLP
159 syndrome.²⁴ Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic
160 conditions and pregnancy complications were identified using ICD-10 codes or data
161 fields abstracted from medical charts to the BCPDR (Table A.1).

162 ***Statistical analyses***

163 The rates of HELLP syndrome per 1000 deliveries were compared between women in
164 each BMI category. Complete case analyses were performed for individuals with known
165 BMI. The association between pre-pregnancy BMI and HELLP syndrome was

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained from a Cox model without adjustment for other risk factors.

Gestational age-specific rates of HELLP syndrome were compared between women in the various BMI categories, using undelivered pregnancies at each gestational week as the denominator. These rates were plotted, and splines with 95% confidence intervals were fitted by the generalized additive model (“gam”) smoothing method. Cox models with interaction terms between pre-pregnancy BMI categories and gestational age at HELLP onset (<34 vs ≥34 weeks’ gestation) were used to obtain crude HRs and 95% CIs. This analysis was carried out to assess whether gestational age at onset modified the association between BMI and HELLP syndrome.

In multivariable analyses, Cox models were also used to adjust for covariates (listed above) and to also examine their associations with early- vs late-onset of HELLP syndrome using interaction terms. We did not assess early- vs late-onset of HELLP syndrome interactions with risk factors including alcohol use and prior adverse birth

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 180 outcomes due to a low number of women with HELLP in these categories, but adjusted
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9 181 for them in the model as potential confounders.

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12 182 Sensitivity analyses included multiple imputations for missing BMI values based
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16 183 on a multiple imputation procedure using SAS statistical software (PROC MI).²⁵
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19 184 Variables included in the imputation were those also included in the regression
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23 185 analyses. Ten imputed datasets were created, with the final results obtained using
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26 186 Rubin's rule.²⁶ All analyses were repeated with the imputed dataset and results were
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30 187 compared with the primary analyses.

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33 188 All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
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37 189 NC) and R version 4.0.3.²⁷ Ethics approval was obtained from the University of British
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40 190 Columbia/Children's and Women's Hospital and Health Centre of British Columbia
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44 191 Research Ethics Board (#H20-03985).

45 46 47 192 *Patient and Public Involvement*

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51 193 Patients or the public WERE NOT involved in the design, or conduct, or reporting, or
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55 194 dissemination plans of our research.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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196 **Results**

197 *Study population*

198 Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,
199 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational
200 age or those with <20 weeks' gestation were excluded (n=14,206, 2.6%). The study
201 population for the primary analyses included 391,941 pregnancies, after exclusion of
202 women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP
203 syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

204 The proportion of women who were in underweight, normal BMI, overweight and
205 obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively.
206 Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes
207 (stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational
208 diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women
209 with overweight and obesity compared with women with normal BMI (Table 1).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

210 Nulliparity and ultrasound diagnosed fetal growth restriction were observed more
211 frequently in the underweight group. Substance use and smoking during pregnancy
212 were more frequent in underweight, overweight, and obese groups compared with
213 women with normal BMI.

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215 *Unadjusted analyses for pre-pregnancy BMI*

216 The rates of HELLP syndrome in women in underweight, normal, overweight, and
217 obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table
218 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and
219 obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),
220 respectively, compared with women who had normal BMI (Table A.2).

221 The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2
222 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,
223 respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks
224 (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 225 maternal age (≥ 35), pre-existing diabetes, chronic hypertension, multiple gestation,
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12 227 use and smoking were higher among women with early-onset vs. late-onset HELLP
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16 228 syndrome. Frequencies of underweight, younger maternal age (< 25 years), nulliparity,
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19 229 IVF conception, and alcohol use were higher among women with late-onset HELLP
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23 230 syndrome (Table A.3).

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26 231 The rates of late-onset HELLP syndrome were higher than early-onset HELLP
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30 232 syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous
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36 234 death, IVF conception, multiple gestation, alcohol use and substance use also had
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40 235 higher rates of late-onset than early-onset HELLP syndrome. Women with multiple
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44 236 gestation had highest rate of HELLP syndrome, followed by those with chronic
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

238 Differences in gestational age-specific incidence rates of HELLP syndrome by
239 BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-
240 age specific rates).

241 Gestational age-specific rates of HELLP syndrome increased over the course of
242 pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women
243 with pre-pregnancy BMI below or above normal values but not among those with normal
244 BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP
245 syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and
246 2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These
247 HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP
248 syndrome, respectively (Table A.2).

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250 *Adjusted analyses*

251 The associations did not change substantially after adjusting for other risk factors (Table
252 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 253 HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly
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9 254 associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP
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12 255 syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).
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15 256 Adjusted hazard ratios (AHR) for each risk factor calculated separately for early-
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19 257 vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly
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22 258 associated with HELLP syndrome included overweight, obesity, advanced maternal age
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26 259 (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation,
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30 260 and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse
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33 261 association with HELLP syndrome. IVF conception was a risk factor for late-onset but
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36 262 not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
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40 263 bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
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44 264 syndrome. Obesity ($p=0.025$), chronic hypertension ($p=0.041$), multiple gestation
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47 265 ($p=0.001$), bleeding before 20 weeks ($p=0.008$) and antepartum bleeding/hemorrhage
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50 266 ($p=0.011$) differed significantly in their associations with early versus late-onset HELLP
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54 267 syndrome (p-values for interaction).
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

268 ***Sensitivity analyses***

269 Women with missing BMI were not substantially different from women with known BMI
270 (Table A.5); and the results were not appreciably changed after the analyses were
271 repeated using imputed BMI values (Table A.6).

273 **Discussion**

274 ***Main findings***

275 To our knowledge, this is the largest contemporary study examining the association
276 between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
277 disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
278 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
279 lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
280 were at elevated risk for developing HELLP syndrome. Obesity was more strongly
281 associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
282 study showed that chronic hypertension, bleeding before 20 weeks' gestation and

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 283 antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP

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8 284 syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP

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15 286 *Interpretation in the context of scientific literature*

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19 287 The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the

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22 288 previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-

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25 289 2016.²⁴ Prior studies describing the association between pre-pregnancy obesity and

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28 290 HELLP syndrome are sparse and results vary. In a retrospective cohort study from a

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31 291 single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal

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34 292 weight was not associated with HELLP syndrome.²⁸ Similarly, a case-control study (n=

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37 293 129 cases and 476 controls) found no association between obesity and HELLP

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40 294 syndrome.²⁹ Furthermore, a retrospective case-control study (including n=687 cases

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43 295 and 601 controls) showed that pre-pregnancy BMI was associated with PE but not

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46 296 HELLP syndrome and suggested that PE and HELLP may have different

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49 297 pathophysiology.¹² In contrast, a population-based cohort study from Norway

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

(n=418,897) found that pre-pregnancy BMI $\geq 30\text{kg/m}^2$ was associated with HELLP syndrome in the first but not the second pregnancy.⁹ However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI. More recently, a population-based study from Canada (n=1,078,323) showed that obesity documented in medical charts was a risk factor for HELLP syndrome,³⁰ however, obesity rates were underestimated and information on BMI was not available, precluding more detailed analyses.

While PE is typically recognized as early- vs late-onset disease (before vs ≥ 34 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is a stronger risk factor for late-onset PE than early-onset PE.¹⁵ That study also demonstrated a correlation between increased prevalence of maternal obesity in parallel with late-onset PE during the 18-year period, while the incidence of early-onset PE stayed relatively constant.¹⁵ In contrast, our study shows a stronger association between overweight/obesity and early-onset HELLP syndrome compared with late-

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5 313 onset HELLP syndrome. This suggests varying pathophysiological pathways between
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9 314 PE and HELLP syndrome or additional obesity-related pathophysiology associated with
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12 315 PE that leads to liver damage at earlier gestation, for instance, obesity-associated
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16 316 steatosis and non-alcoholic fatty liver disease.³¹ We chose the same gestational age
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19 317 cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
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23 318 However, our data suggest an increase in gestational age-specific rates after 28 weeks'
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26 319 gestation in women with obesity and after 30 weeks' gestation in women without
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30 320 obesity. A previous study showed a high proportion of HELLP syndrome cases
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33 321 occurring between 27 and 37 weeks³² which indicates potential dissimilarities with early-
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37 322 vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk factor
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40 323 for early-onset disease for both PE⁶ and HELLP syndrome compared with late-onset
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44 324 disease. It is worth mentioning that the known inverse association between smoking
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47 325 and PE⁶ was also observed in HELLP syndrome in our study, and this warrants further
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51 326 investigations.

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54 327 ***Clinical and research implications***

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 328 Our findings show that increases in gestational age-specific rates of HELLP syndrome
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9 329 vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in
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12 330 women who were in the underweight, overweight and obese categories, but continued
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16 331 increasing in women with normal BMI. This could be due to higher rates of medically
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19 332 indicated early-term deliveries in groups with low or high BMI, which has been shown to
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23 333 reduce maternal morbidity compared with expectant management.³³ It is possible that
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26 334 women whose pre-pregnancy BMI was below and above normal range were more likely
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30 335 to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and
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33 336 delivered at early term (37-38 weeks) to prevent adverse maternal and infant outcomes.
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37 337 In addition to BMI, we also showed that chronic hypertension, bleeding before 20
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40 338 weeks' gestation and antepartum bleeding/hemorrhage were more strongly associated
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44 339 with early- onset HELLP syndrome, while multiple gestation was more strongly
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47 340 associated with late-onset HELLP syndrome. These findings suggest that risk factors for
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51 341 HELLP syndrome have varied clinical relevance based on gestational age at onset of
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54 342 the disease.

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 343 ***Strengths and limitations***

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8 344 The strengths of this study include its population-based design coupled with detailed
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11 345 information about demographic, behavioural and clinical factors that allowed for robust
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15 346 adjustment for possible confounding. We had a large enough sample to provide precise
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19 347 estimates for associations with HELLP syndrome, a rare outcome.
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23 348 This study also has several limitations. First, we did not have detailed information
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26 349 on laboratory values important for the diagnosis of HELLP syndrome and therefore we
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30 350 were not able to estimate the severity of HELLP. We assumed that the diagnosis of
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33 351 HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal
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37 352 condition. However, in milder cases, expectant management with close observation
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40 353 may have led to a delay between the diagnosis and delivery, especially at very preterm
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44 354 gestation. As a result, incidence of early-onset HELLP syndrome may have been
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47 355 underestimated in our study. However, we do not expect a large inaccuracy in this
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51 356 regard because HELLP syndrome is considered a potentially life-threatening condition
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54 357 and delivery is typically not delayed. Second, we did not have information about
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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 358 race/ethnicity, socio-economic status (SES) and prior history of pregnancy with
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9 359 PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding
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12 360 in the assessments of the relation between BMI and HELLP syndrome. However, we
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15 361 adjusted for several possible confounders and did not observe changes in the
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19 362 association between BMI and HELLP syndrome, suggesting that our results are robust.
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22 363 Third, pre-pregnancy BMI was largely self-reported, which may have led to some
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25 364 misclassification. Several validation studies have shown relatively good accuracy of
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29 365 self-reported weight and height for epidemiological studies,^{34–36} suggesting that a large
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33 366 misclassification bias is unlikely. A systematic review of BMI self-report
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37 367 misclassifications showed minimal influence on associations of BMI with pregnancy
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40 368 outcomes.³⁷

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43 369 Approximately 25% of women had missing information about BMI. These women
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47 370 were relatively similar to those with known BMI and sensitivity analyses using imputed
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51 371 BMI values yielded results almost identical to the main analyses. Lastly, the analyses

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 372 examining differences between early- and late-onset HELLP and risk factors other than
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9 373 BMI were exploratory, and further studies are required to confirm our findings.

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15 375 ***Conclusions***

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19 376 Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk
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22 377 factor for HELLP syndrome. However, contrary to the documented association between
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26 378 BMI and PE, with obesity being associated more strongly with late-onset than early-
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29 379 onset PE, our study showed that obesity was more strongly associated with early-onset
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33 380 than with late-onset HELLP syndrome. This information suggests different underlying
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36 381 pathophysiology of the various hypertensive disorders of pregnancy. Our findings can
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40 382 help maternity care providers with regard to pre-pregnancy counselling. Clinicians can
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43 383 better identify women who may benefit from obstetric intervention, as the risk of HELLP
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47 384 increases at late pre-term gestation in all women and continues to increase at term and
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50 385 post-term gestation in women with normal pre-pregnancy BMI. More research on the
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5 386 gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the
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9 387 underlying causes of HELLP syndrome.

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5 389 **Disclosure**

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9 390 The authors report no conflict of interest.

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12 391 **Disclaimer**

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16 392 All inferences, opinions, and conclusions drawn in this publication are those of the
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20 393 authors, and do not reflect the opinions or policies of Perinatal Services BC.

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24 394 **Author Statement/Contribution to Authorship**

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28 395 LW and SL were involved in the conception, planning, carrying out and analyzing data
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31 396 of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.

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35 397 LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ,
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38 398 NR.

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

528 **Tables**529 **Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-**
530 **mass-index; British Columbia, 2008/09-2019/20^a**

	Underweight	Normal BMI	Overweight	Obese
	n = 22,392	n = 231,517	n = 83,864	n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception ^b	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets ^d	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction ^c	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery				
(weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

531 ^aData shown as n(%)

532 ^bIVF = in vitro fertilization

533 ^cUltrasound diagnosed intra-uterine growth restriction (IUGR)

534 ^dInformation on cell numbers <5 was suppressed due to confidentiality reasons.

535 **Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing**
 536 **pregnancies by maternal demographic and clinical characteristics; British Columbia,**
 537 **2008/09-2019/20**

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

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25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death ^a	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception ^b	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use ^a	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

538 ^aInformation on cell numbers <5 was suppressed due to confidentiality reasons. Other
 539 numbers were suppressed if needed to avoid back-calculation from the total

540 ^bIVF = in vitro fertilization

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

542 **Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with**
 543 **95% confidence intervals; British Columbia, 2008/09-2019/20**

	Overall AHR (95% CI) ^a	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P- value ^b
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
≥ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death ^c	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception ^d	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06- 16.87)	8.31 (5.59- 12.35)	17.81 (13.89- 22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (≥ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use ^e	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

544 ^aAHR = adjusted hazard ratio, with 95% confidence interval in parentheses, unless otherwise
 545 specified

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

^bp-value for interaction with early- vs late-onset HELLP syndrome.

^cN/A = not applicable. We did not examine differences by early- vs late-onset for prior stillbirth/neonatal death or alcohol use due to small sample size.

^dIVF = in vitro fertilization

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Figure legend

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Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category

(Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were

combined. Splines with 95% confidence intervals were fitted by the generalized additive

model (“gam”) smoothing method.

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Supplemental Figure 1. Flowchart of study sample selection.

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 578 **Supplementary tables**

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9 579 **Supplemental Table 1. Definitions and sources of variables**

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used; Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used; or 'E10','E11', 'O245','O246','O247'	BCPDR ICD-10

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

 Chronic

'O10','O11'

ICD-10

hypertension

 Mother had at least one prior live born infant, who died

Prior stillbirth within the first 28 days of life.

BCPDR

/neonatal death Mother had at least one prior stillbirth or intrauterine death documented.

 IVF conception Mother had in-vitro fertilization to achieve the current pregnancy.

BCPDR

 Multiple gestation The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABOURS.

BCPDR

 Antepartum

bleeding

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.

BCPDR

Antepartum

Mother had any antepartum hemorrhage or bleeding in bleeding or hemorrhage \geq 20 weeks weeks

pregnancy \geq 20 weeks gestation, including bleeding from BCPDR cervical polyps.

Intrauterine Growth Restriction^a

Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.

Gestational Hypertension

Care provider diagnosed mother with gestational hypertension during the current pregnancy.

BCPDR

Gestational Diabetes

Gestational diabetes, insulin dependent.

Gestational diabetes, non-insulin dependent.

BCPDR

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	BCPDR
Substance use	Mother used any of the following substances at any time during the current pregnancy: heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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5 Mother was diagnosed with HELLP Syndrome (H-
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9 HELLP syndrome hemolysis, EL-elevated liver enzymes, LP-low platelet BCPDR
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16 580 ^aUltrasound diagnosed intra-uterine growth restriction (IUGR)
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

582 **Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and**
 583 **hazard ratios with 95% confidence intervals**

	Underweight	Normal BMI	Overweight	Obese
<i>All pregnancies</i>				
N cases (rate per thousand) ^a	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR ^b	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
<i>Early-onset HELLP (< 34 wks)</i>				
N cases (rate per thousand) ^a	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR ^b	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Late-onset HELLP (≥ 34 *wks)*

N cases (rate per

35 (1.6) 462 (2.0) 199 (2.4) 145 (2.8)

thousand)^a

0.81 (0.57- 1.21 (1.02- 1.42 (1.17-

Crude HR^b

Ref

1.14) 1.42) 1.71)

584 ^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34
 585 weeks gestation (late-onset HELLP).

586 ^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise
 587 specified

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

589 **Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs**
 590 **late-onset HELLP syndrome; British Columbia, 2008/09-2019/20^a**

	Early-onset	Late-onset
	HELLP	HELLP
	n =275	n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)
Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death ^b	<5 (<1.8)	<5 (<0.5)
IVF conception ^c	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use ^b	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

591 ^aData shown as n(%)

592 ^bInformation on cell numbers <5 was suppressed due to confidentiality reasons.

593 ^cIVF = in vitro fertilization

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

598 **Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per**
 599 **1000 ongoing pregnancies)^a**

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
	<5/22392	<5/231517	<5/83864	<5/54168
20-21	(<0.22)	(<0.02)	(<0.06)	(<0.09)
	<5/22379	<5/231351	<5/83796	<5/54108
22-23	(<0.22)	(<0.02)	(<0.06)	(<0.09)
	<5/22356	6/231174 (0.03)	<5/83720	5/54023 (0.09)
24-25	(<0.22)		(<0.06)	
	<5/22332	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
26-27	(<0.22)			
	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
28-29				
	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)
30-31				

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
		116/227212		
34-35	10/21902 (0.46)		58/81998 (0.71)	42/52652 (0.80)
		(0.51)		
		154/221075		
36-37	13/21247 (0.61)		70/79515 (0.88)	55/50825 (1.08)
		(0.70)		
		131/189757		
38-39	11/17845 (0.62)		56/66951 (0.84)	36/40911 (0.88)
		(0.69)		
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

^aInformation on cell numbers <5 was suppressed due to confidentiality reasons.

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 602 **Supplemental Table 5. Demographic and clinical characteristics of women missing pre-**

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9 603 **pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20^a**

	BMI not missing	BMI missing
	n = 391,941	n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception ^b	11549 (3.0)	3877 (2.9)
Multiple gestation		

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Twins	5806 (1.5)	2478 (1.9)
Triplets/Quadruplets	82 (0)	27 (0)
Antepartum bleeding/hemorrhage		
< 20 weeks	7337 (1.9)	1813 (1.4)
≥ 20 weeks	5659 (1.4)	1496 (1.1)
Intrauterine Growth Restriction ^c	8857 (2.3)	2471 (1.9)
Gestational Hypertension	21124 (5.4)	6623 (5.0)
Gestational Diabetes	44172 (11.3)	13248 (10.0)
Proteinuria	21124 (5.4)	6623 (5.0)
Alcohol use	4162 (1.1)	1845 (1.4)
Substance use	15701 (4.0)	6758 (5.1)
Smoking	26401 (6.7)	10435 (7.9)
Second-hand smoke	26319 (6.7)	7565 (5.7)

^aData shown as n(%)

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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5 ^bIVF = in vitro fertilization
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9 ^cUltrasound diagnosed intra-uterine growth restriction (IUGR)
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

606 **Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data**
 607 **for missing values of BMI**

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand) ^a	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR ^b	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) ^a	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

		1.24 (0.92-	
	0.96 (0.51-1.8) Ref		1.46 (1.03-2.08)
Adjusted HR ^b		1.66)	

^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified.

Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro

fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use,

smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

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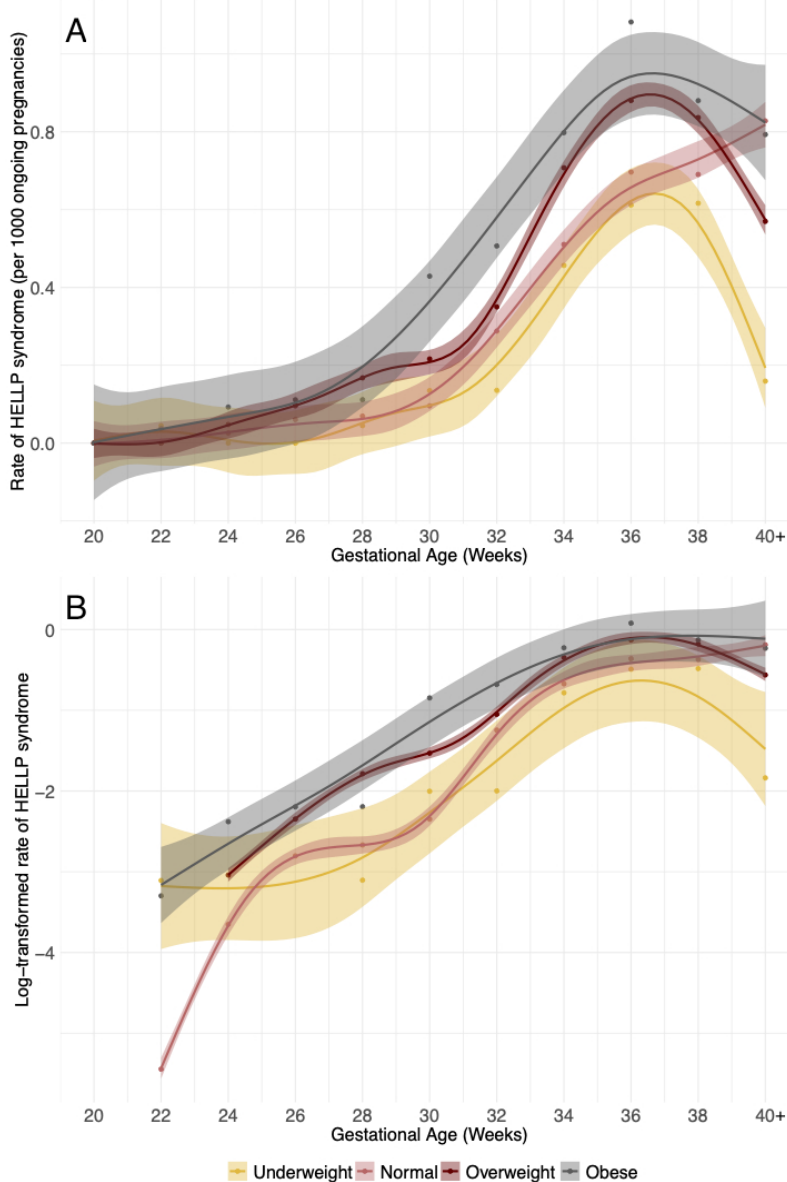
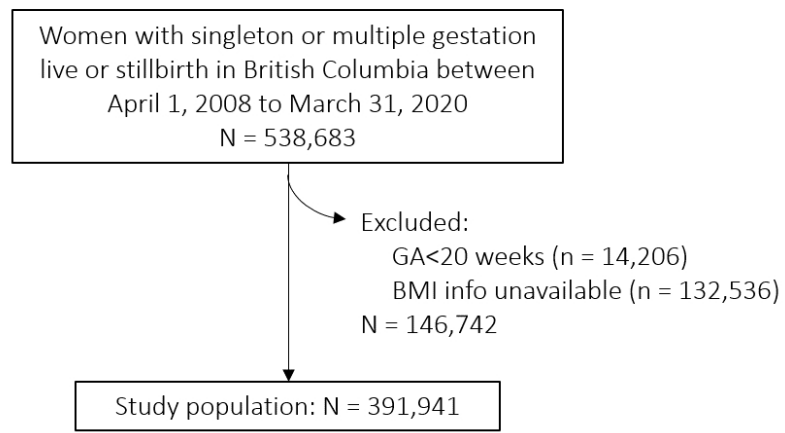


Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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Supplemental Figure 1. Flowchart of study sample selection.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title page	"Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study."
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	31	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 - 147
		(b) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 - 147
		(c) Explain how missing data were addressed	6-7	Lines 123 - 147
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	N/A	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	N/A	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-29, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(b) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-23	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-23	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

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Manuscript ID	bmjopen-2023-079131.R1
Article Type:	Original research
Date Submitted by the Author:	30-Jan-2024
Complete List of Authors:	Wang, Li Qing; The University of British Columbia Faculty of Medicine, Department of Obstetrics and Gynaecology; BC Children's Hospital Research Institute Bone, Jeffrey; BC Children's Hospital Research Institute, Research Informatics Muraca, Giulia M; Hamilton, Department of Obstetrics and Gynecology Razaz, Neda; Karolinska Institute, Clinical Epidemiology Division, Department of Medicine Solna Joseph, K.S.; The University of British Columbia Faculty of Medicine, Department of Obstetrics and Gynaecology, School of Population and Public Health; BC Children's Hospital Research Institute Lisonkova, Sarka; The University of British Columbia Faculty of Medicine, Obstetrics and Gynaecology, School of Population and Public Health; BC Children's Hospital Research Institute
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Obesity, EPIDEMIOLOGY, OBSTETRICS

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4 1 **Title:** Pre-pregnancy body mass index and other risk factors for early- and late-onset
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7 2 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-
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9
10 3 based retrospective cohort study.

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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27 24 **Abstract**

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31 25 **Background:** Obesity increases risk of pre-eclampsia, but the association with
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35 26 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
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38 27 understudied.

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42 28 **Objective:** To examine the association between pre-pregnancy body-mass-index (BMI)
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45 29 and HELLP syndrome, including early- vs. late-onset disease.

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48 30 **Study Design:** A retrospective cohort study using population-based data.

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52 31 **Setting:** British Columbia (BC), Canada, 2008/09-2019/20.

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55 32 **Population:** All pregnancies resulting in live births or stillbirths at ≥ 20 weeks' gestation.

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 33 **Methods:** BMI categories (kg/m²) included: underweight (<18.5), normal (18.5-24.9),
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9 34 overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP
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12 35 syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing
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15 36 pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to
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19 37 assess the associations between risk factors (e.g., BMI, maternal age and parity) and
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22 38 early- vs late-onset HELLP syndrome.

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26 39 **Main outcome measures:** Early- and late-onset HELLP syndrome.

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29 40 **Results:** The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases
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33 41 among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI,
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36 42 overweight and obese categories, respectively. Overall, gestational age-specific rates of
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40 43 HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal
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43 44 BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard
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46 45 ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP
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50 46 syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also showed differing AHRs between early- vs. late-onset HELLP syndrome.

Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the association is stronger with early-onset HELLP syndrome. Associations with early- and late-onset HELLP syndrome differed for some risk factors, suggesting possible differences in etiologic mechanisms.

Strengths and limitations of this study

- We were able to describe gestational age-specific incidence of HELLP syndrome, based on population data on all pregnancies.
- The population-based design coupled with detailed information about demographic, behavioural and clinical factors allowed robust adjustment for possible confounding.
- We did not have detailed information on laboratory values used for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP syndrome.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

- 62 • We did not have information about race/ethnicity, socio-economic status (SES)
63 and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- 64 • Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had
65 missing information about BMI. We used multiple imputation methods to address
66 this limitation.

68 **Key words**

69 Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity,
70 pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP
71 syndrome.

72 **Word count:** 3036

74 **Introduction**

75 Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the
76 leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

77 worldwide(1,2) and accounting for up to 14% of maternal deaths.(3) Early-onset PE at
78 <34 weeks' gestation is often associated with placental insufficiency whereas late-onset
79 PE is often associated with pre-existing maternal health conditions such as metabolic
80 syndrome and obesity.(4) Early- vs late-onset PE differ with regard to some risk factors,
81 clinical management and rates of adverse perinatal outcomes.(5,6) A related condition,
82 namely, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs
83 in 0.2-0.8% of pregnancies(7–9) and 10-20% of cases of severe PE.(10) Although
84 HELLP syndrome has been distinguished from PE as a separate disease,(11) it is still
85 commonly viewed as a form of severe PE.(9) While the distinction between early- and
86 late-onset PE and the difference in the associations between pre-pregnancy obesity and
87 these conditions has been established, such differences have not been studied with
88 regard to HELLP syndrome.

89 Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–
90 15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the
91 proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

92 prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18)
93 and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in
94 high income countries, the association between maternal pre-pregnancy body-mass-
95 index (BMI) and HELLP syndrome has not been adequately assessed in a large
96 population-based study to date.

97 We carried out a population-based, retrospective cohort study to examine the
98 association between maternal pre-pregnancy BMI and HELLP syndrome and to assess
99 differences in this association in early- vs late-onset HELLP syndrome. We
100 hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this
101 relationship may be different in early- compared with late-onset disease. In additional
102 analyses, we examined other risk factors for HELLP syndrome in terms of their
103 association with early- vs late-onset HELLP syndrome.

104 **Materials and Methods**

105 *Data sources and study population*

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 106 The study included all live births and stillbirths at ≥ 20 weeks' gestation in British
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9 107 Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from
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11
12 108 the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes
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16 109 information on >99% of births in BC, with detailed data on maternal demographic
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19 110 characteristics, prenatal care, pregnancy complications, labor and delivery
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23 111 characteristics and neonatal outcomes. Each record, abstracted from medical charts (or
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26 112 midwives' notes), includes up to 25 International Classification of Diseases, 10th Edition,
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30 113 Canadian version (ICD-10-CA) codes for diagnoses related to the delivery
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33 114 hospitalization. Chart abstraction is standardized and conducted by trained personnel,
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37 115 and data quality is routinely assessed. Prior validation studies showed high accuracy of
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40 116 collected information on labor and delivery.(21)

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44 117 ***Pre-pregnancy BMI and HELLP syndrome***

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48 118 Pre-pregnancy weight and height were based on maternal self-report or health care
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51 119 provider assessment at ≤ 11 weeks' gestation.(22) BMI was classified as follows (in
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55 120 kg/m²): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

121 (≥30.0).(23) The primary outcome of this study was a physician diagnosis of HELLP
122 syndrome documented in the medical chart, and abstracted and recorded in the
123 BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee
124 classification criteria, namely lactate dehydrogenase ≥600 IU/l, liver transaminases
125 (aspartate aminotransferase and alanine aminotransferase) elevated more than twice the
126 upper limit of normal, and a platelet count <100,000/ μ l (109/l).(24) Early- and late-onset
127 HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks and
128 ≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to ascertain
129 gestational age, and the last menstrual period estimate of gestational age was used for
130 those without early pregnancy ultrasound information.

131 *Covariates*

132 In addition to BMI, we examined the association between maternal age, nulliparity, pre-
133 existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple
134 gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance
135 use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 136 use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as
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9 137 potential confounders; all these factors are known to be associated with HELLP
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12 138 syndrome.(25) Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic
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16 139 conditions and pregnancy complications were identified using ICD-10 codes or data
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19 140 fields abstracted from medical charts to the BCPDR (Table A.1).

22 141 *Statistical analyses*

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26 142 The rates of HELLP syndrome per 1000 deliveries were compared between women in
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30 143 each BMI category. Complete case analyses were performed for individuals with known
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33 144 BMI. The association between pre-pregnancy BMI and HELLP syndrome was first
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37 145 expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained
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40 146 from a Cox model without adjustment for other risk factors.

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43 147 Gestational age-specific rates of HELLP syndrome were compared between
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47 148 women in the various BMI categories, using undelivered pregnancies at each
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50 149 gestational week as the denominator. These rates were plotted, and splines with 95%
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54 150 confidence intervals were fitted by the generalized additive model (“gam”) smoothing
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

151 method. Cox models with interaction terms between pre-pregnancy BMI categories and
152 gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain
153 crude HRs and 95% CIs. This analysis was carried out to assess whether gestational
154 age at onset modified the association between BMI and HELLP syndrome.

155 In multivariable analyses, Cox models were also used to adjust for covariates
156 (listed above) and to also examine their associations with early- vs late-onset of HELLP
157 syndrome using interaction terms. We did not assess early- vs late-onset of HELLP
158 syndrome interactions with risk factors including alcohol use and prior adverse birth
159 outcomes due to a low number of women with HELLP syndrome in these categories,
160 but adjusted for them in the model as potential confounders.

161 Sensitivity analyses included multiple imputations for missing BMI values based
162 on a multiple imputation procedure using SAS statistical software (PROC MI).(26)
163 Variables included in the imputation were those also included in the regression
164 analyses. Ten imputed datasets were created, with the final results obtained using

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 165 Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were
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9 166 compared with the primary analyses.

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12 167 All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
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16 168 NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British
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19 169 Columbia/Children's and Women's Hospital and Health Centre of British Columbia
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22
23 170 Research Ethics Board (#H20-03985).

24 25 26 171 *Patient and Public Involvement*

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30 172 Neither patients nor the public were involved in the design, or conduct, or reporting, or
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34 173 dissemination plans of our research.

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38 39 40 175 **Results**

41 42 43 176 *Study population*

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48 177 Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,
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51 178 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational
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55 179 age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

180 study population for the primary analyses included 391,941 pregnancies, after exclusion
181 of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP
182 syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

183 The proportion of women who were in underweight, normal BMI, overweight and
184 obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively.

185 Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes
186 (stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational
187 diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women
188 with overweight and obesity compared with women with normal BMI (Table 1).

189 Nulliparity and ultrasound diagnosed fetal growth restriction were observed more
190 frequently in the underweight group. Substance use and smoking during pregnancy
191 were more frequent in underweight, overweight, and obese groups compared with
192 women with normal BMI.

193

194 *Unadjusted analyses for pre-pregnancy BMI*

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

195 The rates of HELLP syndrome in women in underweight, normal, overweight, and
196 obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table
197 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and
198 obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),
199 respectively, compared with women who had normal BMI (Table A.2).

200 The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2
201 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,
202 respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks
203 (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older
204 maternal age (≥ 35), pre-existing diabetes, chronic hypertension, multiple gestation,
205 bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance
206 use and smoking were higher among women with early-onset vs. late-onset HELLP
207 syndrome. Frequencies of underweight, younger maternal age (< 25 years), nulliparity,
208 IVF conception, and alcohol use were higher among women with late-onset HELLP
209 syndrome (Table A.3).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

210 The rates of late-onset HELLP syndrome were higher than early-onset HELLP
211 syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous
212 women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal
213 death, IVF conception, multiple gestation, alcohol use and substance use also had
214 higher rates of late-onset than early-onset HELLP syndrome. Women with multiple
215 gestation had highest rate of HELLP syndrome, followed by those with chronic
216 hypertension.

217 Differences in gestational age-specific incidence rates of HELLP syndrome by
218 BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-
219 age specific rates).

220 Gestational age-specific rates of HELLP syndrome increased over the course of
221 pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women
222 with pre-pregnancy BMI below or above normal values but not among those with normal
223 BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP
224 syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP syndrome, respectively (Table A.2).

Adjusted analyses

The associations did not change substantially after adjusting for other risk factors (Table 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).

Adjusted hazard ratios (AHR) for each risk factor calculated separately for early- vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly associated with HELLP syndrome included overweight, obesity, advanced maternal age (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation, and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

240 association with HELLP syndrome. IVF conception was a risk factor for late-onset but
241 not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
242 bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
243 syndrome. Obesity ($p=0.025$), chronic hypertension ($p=0.041$), multiple gestation
244 ($p=0.001$), bleeding before 20 weeks ($p=0.008$) and antepartum bleeding/hemorrhage
245 ($p=0.011$) differed significantly in their associations with early versus late-onset HELLP
246 syndrome (p-values for interaction).

247 *Sensitivity analyses*

248 Women with missing BMI were not substantially different from women with known BMI
249 (Table A.5); and the results were not appreciably changed after the analyses were
250 repeated using imputed BMI values (Table A.6).

251

252 **Discussion**

253 *Main findings*

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

254 To our knowledge, this is the largest contemporary study examining the association
255 between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
256 disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
257 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
258 lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
259 were at elevated risk for developing HELLP syndrome. Obesity was more strongly
260 associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
261 study showed that chronic hypertension, bleeding before 20 weeks' gestation and
262 antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP
263 syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP
264 syndrome.

Interpretation in the context of scientific literature

266 The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the
267 previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-
268 2016.⁽²⁵⁾ Prior studies describing the association between pre-pregnancy obesity and

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

HELLP syndrome are sparse and results vary. In a retrospective cohort study from a single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal weight was not associated with HELLP syndrome.(29) Similarly, a case-control study (n= 129 cases and 476 controls) found no association between obesity and HELLP syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases and 601 controls) showed that pre-pregnancy BMI was associated with PE but not HELLP syndrome and suggested that PE and HELLP may have different pathophysiology.(12) In contrast, a population-based cohort study from Norway (n=418,897) found that pre-pregnancy BMI $\geq 30\text{kg/m}^2$ was associated with HELLP syndrome in the first but not the second pregnancy.(9) However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI. More recently, a population-based study from Canada (n=1,078,323) showed that obesity documented in medical charts was a risk factor for HELLP syndrome,(31) however, obesity rates were underestimated and information on BMI was not available, precluding more detailed analyses.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

284 While PE is typically recognized as early- vs late-onset disease (before vs \geq 34
285 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A
286 prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is
287 a stronger risk factor for late-onset PE than early-onset PE.(15) That study also
288 demonstrated a correlation between increased prevalence of maternal obesity in
289 parallel with late-onset PE during the 18-year period, while the incidence of early-onset
290 PE stayed relatively constant.(15) In contrast, our study shows a stronger association
291 between overweight/obesity and early-onset HELLP syndrome compared with late-
292 onset HELLP syndrome. This suggests varying pathophysiological pathways between
293 PE and HELLP syndrome or additional obesity-related pathophysiology associated with
294 PE that leads to liver damage at earlier gestation, for instance, obesity-associated
295 steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age
296 cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
297 However, our data suggest an increase in gestational age-specific rates after 28 weeks'
298 gestation in women with obesity and after 30 weeks' gestation in women without

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

299 obesity. A previous study showed a high proportion of HELLP syndrome cases
300 occurring between 27 and 37 weeks,(33) which indicates potential dissimilarities with
301 early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk
302 factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-
303 onset disease. It is worth mentioning that the known inverse association between
304 smoking and PE(6) was also observed in HELLP syndrome in our study, and this
305 warrants further investigation.

Clinical and research implications

307 Our findings show that increases in gestational age-specific rates of HELLP syndrome
308 vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in
309 women who were in the underweight, overweight and obese categories, but continued
310 increasing in women with normal BMI. This could be due to higher rates of medically
311 indicated early-term deliveries in groups with low or high BMI, which has been shown to
312 reduce maternal morbidity compared with expectant management.(34) It is possible that
313 women whose pre-pregnancy BMI was below and above normal range were more likely

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

314 to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and
315 therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal
316 and infant outcomes. However, further research is needed to confirm this hypothesis. In
317 addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks'
318 gestation and antepartum bleeding/hemorrhage were more strongly associated with
319 early-onset HELLP syndrome, while multiple gestation was more strongly associated
320 with late-onset HELLP syndrome. The association between bleeding at <20 weeks gestation
321 and early-onset HELLP syndrome is novel. Such bleeding can be caused by abnormal
322 placental conditions (e.g., abnormal implantation and associated bleeding), which may
323 play a role in the development of HELLP syndrome. These findings are exploratory and
324 require confirmation by other studies. However, they raise the intriguing possibility that
325 determinants of HELLP syndrome (such as antepartum bleeding) have different
326 associations with early and late onset HELLP syndrome depending on whether they
327 occur at <20 weeks or at ≥ 20 weeks' gestation. In our study, the association between
328 antepartum bleeding at ≥ 20 weeks' gestation and HELLP syndrome (which could

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 329 have been explained as being a consequence of HELLP syndrome causing placental
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9 330 abruption) was not significant in adjusted models.

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12 331 ***Strengths and limitations***

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15 332 The strengths of this study include its population-based design coupled with detailed
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19 333 information about demographic, behavioural and clinical factors that allowed for robust
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22 334 adjustment for possible confounding. We had a large enough sample to provide precise
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26 335 estimates for associations with HELLP syndrome, a rare outcome.

27
28
29 336 This study also has several limitations. First, we did not have detailed information
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33 337 on laboratory values important for the diagnosis of HELLP syndrome and therefore we
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37 338 were not able to estimate the severity of HELLP. We assumed that the diagnosis of
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40 339 HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal
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44 340 condition. However, in milder cases, expectant management with close observation
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47 341 may have led to a delay between the diagnosis and delivery, especially at very preterm
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50 342 gestation. As a result, incidence of early-onset HELLP syndrome may have been
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54 343 underestimated in our study. However, we do not expect a large inaccuracy in this

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

344 regard because HELLP syndrome is considered a potentially life-threatening condition
345 and delivery is typically not delayed. Second, we did not have information about
346 race/ethnicity, socio-economic status (SES) and prior history of pregnancy with
347 PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding
348 in the assessments of the relation between BMI and HELLP syndrome. However, we
349 adjusted for several possible confounders and did not observe changes in the
350 association between BMI and HELLP syndrome, suggesting that our results are robust.
351 Third, pre-pregnancy BMI was largely self-reported, which may have led to some
352 misclassification. Several validation studies have shown relatively good accuracy of
353 self-reported weight and height for epidemiological studies,(35–37) suggesting that a
354 large misclassification bias is unlikely. A systematic review of BMI self-report
355 misclassification showed minimal influence on associations between BMI and
356 pregnancy outcomes.(38)

357 Approximately 25% of women had missing information about BMI. These women
358 were relatively similar to those with known BMI and sensitivity analyses using imputed

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 359 BMI values yielded results almost identical to the main analyses. Lastly, the analyses
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9 360 examining differences between early- and late-onset HELLP and risk factors other than
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12 361 BMI were exploratory, and further studies are required to confirm our findings.
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19 363 ***Conclusions***

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22 364 Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk
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26 365 factor for HELLP syndrome. However, contrary to the documented association between
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30 366 BMI and PE, with obesity being associated more strongly with late-onset than early-
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33 367 onset PE, our study showed that obesity was more strongly associated with early-onset
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37 368 than with late-onset HELLP syndrome. This suggests potentially different underlying
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40 369 pathophysiology for the various hypertensive disorders of pregnancy. Our findings can
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44 370 help maternity care providers with regard to pre-pregnancy counselling. Clinicians can
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47 371 better identify women who may benefit from obstetric intervention, as the risk of HELLP
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51 372 increases at late pre-term gestation in all women and continues to increase at term and
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54 373 post-term gestation in women with normal pre-pregnancy BMI. More research on the
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5 374 gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the

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9 375 underlying causes of HELLP syndrome.

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5 377 **Disclosure**

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9 378 The authors report no conflict of interest.

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12 379 **Disclaimer**

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16 380 All inferences, opinions, and conclusions drawn in this publication are those of the

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20 381 authors, and do not reflect the opinions or policies of Perinatal Services BC.

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24 382 **Author Statement/Contribution to Authorship**

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28 383 LW and SL were involved in the conception, planning, carrying out and analyzing data

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32 384 of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.

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35 385 LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ,

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39 386 NR.

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33 399 **Competing interests statement**

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36 400 The authors report no conflict of interest.

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40 401 **Data availability**

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43 402 Data may be obtained from a third party and are not publicly available.
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47 403 **Ethics Approval Statement**
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5 404 Ethics approval was obtained from the University of British Columbia/Children's and

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9 405 Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

528 **Tables**529 **Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-**
530 **mass-index; British Columbia, 2008/09-2019/20^a**

	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception ^b	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets ^d	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction ^c	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

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Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery				
(weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

531 ^aData shown as n(%)

532 ^bIVF = in vitro fertilization

533 ^cUltrasound diagnosed intra-uterine growth restriction (IUGR)

534 ^dInformation on cell numbers <5 was suppressed due to confidentiality reasons.

535 **Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing**
 536 **pregnancies by maternal demographic and clinical characteristics; British Columbia,**
 537 **2008/09-2019/20**

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death ^a	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception ^b	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use ^a	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

538 ^aInformation on cell numbers <5 was suppressed due to confidentiality reasons. Other
 539 numbers were suppressed if needed to avoid back-calculation from the total

540 ^bIVF = in vitro fertilization

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

542 **Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with**
 543 **95% confidence intervals; British Columbia, 2008/09-2019/20**

	Overall AHR (95% CI) ^a	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P- value ^b
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
≥ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death ^c	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception ^d	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06- 16.87)	8.31 (5.59- 12.35)	17.81 (13.89- 22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (≥ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use ^e	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

544 ^aAHR = adjusted hazard ratio, with 95% confidence interval in parentheses, were obtained from
 545 the Cox model that included all variables in the table.

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^bp-value for interaction with early- vs late-onset HELLP syndrome.

^cN/A = not applicable. We did not examine differences by early- vs late-onset for prior stillbirth/neonatal death or alcohol use due to small sample size.

^dIVF = in vitro fertilization

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555 **Figure legend**

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557 **Figure 1.** Gestational-age specific rates of HELLP syndrome for each BMI category

558 (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were

559 combined. Splines with 95% confidence intervals were fitted by the generalized additive

560 model (“gam”) smoothing method.

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562 **Supplemental Figure 1.** Flowchart of study sample selection.

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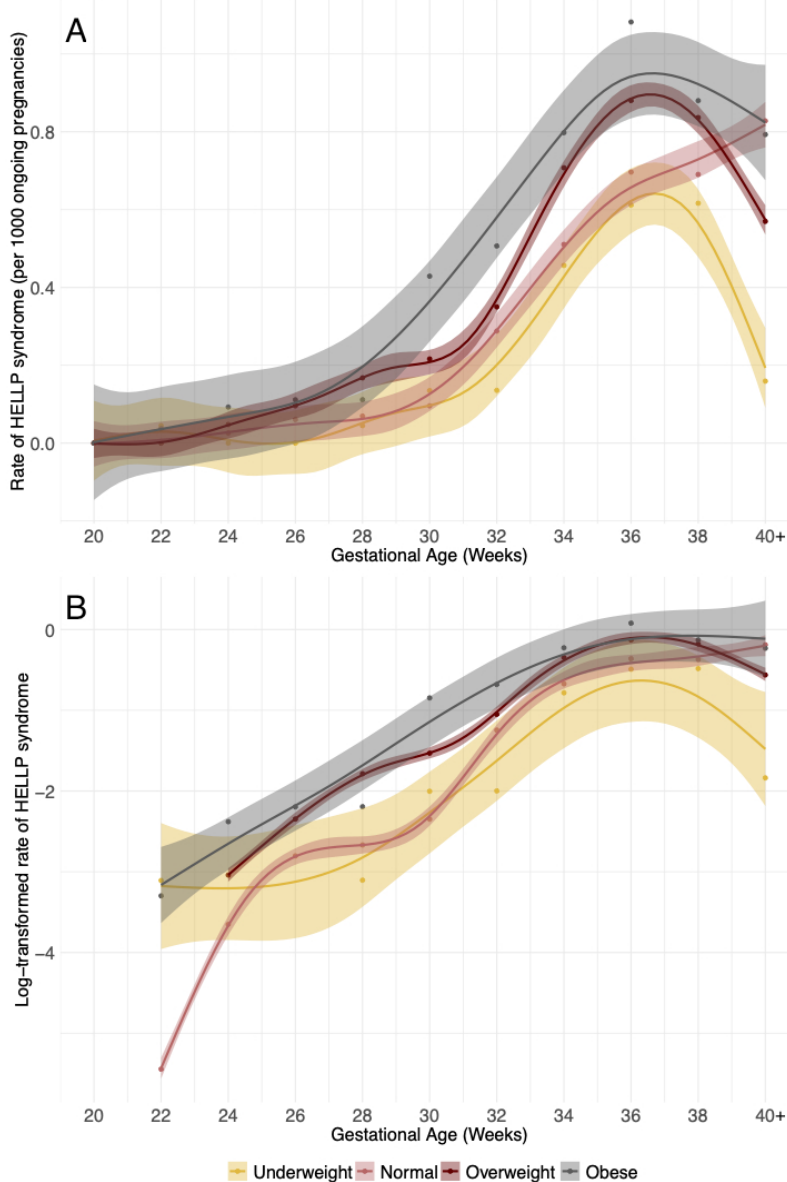
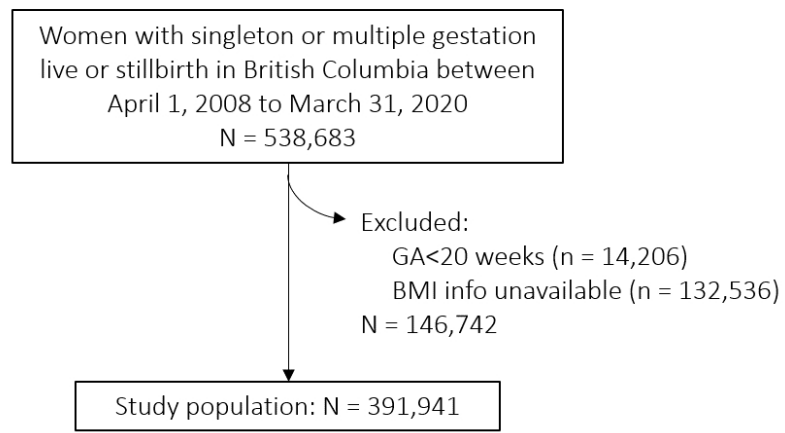


Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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Supplemental Figure 1. Flowchart of study sample selection.

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Supplementary tables

Supplemental Table 1. Definitions and sources of variables

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used; or 'E10','E11', 'O245','O246','O247'	ICD-10
Chronic hypertension	'O10','O11'	ICD-10
Prior stillbirth	Mother had at least one prior live born infant, who died within the first 28 days of life.	BCPDR
/neonatal death	Mother had at least one prior stillbirth or intrauterine death documented.	
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPDR
Multiple gestation	The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABORS.	BCPDR

Antepartum bleeding		
< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	BCPDR
Antepartum bleeding or hemorrhage ≥ 20 weeks	Mother had any antepartum hemorrhage or bleeding in pregnancy ≥ 20 weeks gestation, including bleeding from cervical polyps.	BCPDR
Intrauterine Growth Restriction ^a	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.	BCPDR
Gestational Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	BCPDR
Gestational Diabetes	Gestational diabetes, insulin dependent. Gestational diabetes, non-insulin dependent.	BCPDR
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother’s use of alcohol as a risk factor in this pregnancy.	BCPDR

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Substance use	Mother used any of the following substances at any time during the current pregnancy: heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
HELLP syndrome	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low platelet count)	BCPDR

^aUltrasound diagnosed intra-uterine growth restriction (IUGR)

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Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and hazard ratios with 95% confidence intervals

	Underweight	Normal BMI	Overweight	Obese
<i>All pregnancies</i>				
N cases (rate per thousand) ^a	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR ^b	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
<i>Early-onset HELLP (< 34 wks)</i>				
N cases (rate per thousand) ^a	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR ^b	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)
<i>Late-onset HELLP (≥ 34 wks)</i>				
N cases (rate per thousand) ^a	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR ^b	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	1.42 (1.17-1.71)

^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34 weeks gestation (late-onset HELLP).

^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs late-onset HELLP syndrome; British Columbia, 2008/09-2019/20^a

	Early-onset HELLP	Late-onset HELLP
	n =275	n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)
Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)

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Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death ^b	<5 (<1.8)	<5 (<0.5)
IVF conception ^c	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use ^b	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

^aData shown as n(%)

^bInformation on cell numbers <5 was suppressed due to confidentiality reasons.

^cIVF = in vitro fertilization

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Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per 1000 ongoing pregnancies)^a

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	<5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	<5/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	<5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)
32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
34-35	10/21902 (0.46)	116/227212 (0.51)	58/81998 (0.71)	42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	55/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	36/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

^aInformation on cell numbers <5 was suppressed due to confidentiality reasons.

Supplemental Table 5. Demographic and clinical characteristics of women missing pre-pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20^a

	BMI not missing	BMI missing
	n = 391,941	n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception ^b	11549 (3.0)	3877 (2.9)
Multiple gestation		
Twins	5806 (1.5)	2478 (1.9)

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3	Triplets/Quadruplets	82 (0)	27 (0)
4			
5			
6	Antepartum bleeding/hemorrhage		
7			
8	< 20 weeks	7337 (1.9)	1813 (1.4)
9			
10	≥ 20 weeks	5659 (1.4)	1496 (1.1)
11			
12			
13	Intrauterine Growth Restriction ^c	8857 (2.3)	2471 (1.9)
14			
15			
16	Gestational Hypertension	21124 (5.4)	6623 (5.0)
17			
18	Gestational Diabetes	44172 (11.3)	13248 (10.0)
19			
20			
21	Proteinuria	21124 (5.4)	6623 (5.0)
22			
23	Alcohol use	4162 (1.1)	1845 (1.4)
24			
25			
26	Substance use	15701 (4.0)	6758 (5.1)
27			
28	Smoking	26401 (6.7)	10435 (7.9)
29			
30			
31	Second-hand smoke	26319 (6.7)	7565 (5.7)
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^aData shown as n(%)

^bIVF = in vitro fertilization

^cUltrasound diagnosed intra-uterine growth restriction (IUGR)

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Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data for missing values of BMI

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand) ^a	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR ^b	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) ^a	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)
Adjusted HR ^b	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2.08)

^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title page	"Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study."
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	31	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

Continued on next page

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 - 147
		(b) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 - 147
		(c) Explain how missing data were addressed	6-7	Lines 123 - 147
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	N/A	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-29, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(b) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study in British Columbia, Canada.

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1 **Title:** Pre-pregnancy body mass index and other risk factors for early- and late-onset
2 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-
3 based retrospective cohort study in British Columbia, Canada.

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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27 24 **Abstract**

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31 25 **Background:** Obesity increases risk of pre-eclampsia, but the association with
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35 26 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
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38 27 understudied.

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42 28 **Objective:** To examine the association between pre-pregnancy body-mass-index (BMI)
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45 29 and HELLP syndrome, including early- vs. late-onset disease.

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48 30 **Study Design:** A retrospective cohort study using population-based data.

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52 31 **Setting:** British Columbia (BC), Canada, 2008/09-2019/20.

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55 32 **Population:** All pregnancies resulting in live births or stillbirths at ≥ 20 weeks' gestation.

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 33 **Methods:** BMI categories (kg/m²) included: underweight (<18.5), normal (18.5-24.9),
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9 34 overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP
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12 35 syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing
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15 36 pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to
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19 37 assess the associations between risk factors (e.g., BMI, maternal age and parity) and
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22 38 early- vs late-onset HELLP syndrome.

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26 39 **Main outcome measures:** Early- and late-onset HELLP syndrome.

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29 40 **Results:** The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases
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33 41 among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI,
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36 42 overweight and obese categories, respectively. Overall, gestational age-specific rates of
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40 43 HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal
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43 44 BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard
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46 45 ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP
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50 46 syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also showed differing AHRs between early- vs. late-onset HELLP syndrome.

Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the association is stronger with early-onset HELLP syndrome. Associations with early- and late-onset HELLP syndrome differed for some risk factors, suggesting possible differences in etiologic mechanisms.

Strengths and limitations of this study

- We were able to describe gestational age-specific incidence of HELLP syndrome, based on population data on all pregnancies.
- The population-based design coupled with detailed information about demographic, behavioural and clinical factors allowed robust adjustment for possible confounding.
- We did not have detailed information on laboratory values used for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP syndrome.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

- 62 • We did not have information about race/ethnicity, socio-economic status (SES)
63 and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- 64 • Approximately 25% of women had missing information about BMI, and we used
65 multiple imputation methods to address this limitation.

67 **Key words**

68 Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity,
69 pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP
70 syndrome.

71 **Word count: 3036**

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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81 Introduction

82 Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the

83 leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies

84 worldwide(1,2) and accounting for up to 14% of maternal deaths.(3) Early-onset PE at

85 <34 weeks' gestation is often associated with placental insufficiency whereas late-onset

86 PE is often associated with pre-existing maternal health conditions such as metabolic

87 syndrome and obesity.(4) Early- vs late-onset PE differ with regard to some risk factors,

88 clinical management and rates of adverse perinatal outcomes.(5,6) A related condition,

89 namely, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs

90 in 0.2-0.8% of pregnancies(7-9) and 10-20% of cases of severe PE.(10) Although

91 HELLP syndrome has been distinguished from PE as a separate disease,(11) it is still

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

92 commonly viewed as a form of severe PE.(9) While the distinction between early- and
93 late-onset PE and the difference in the associations between pre-pregnancy obesity and
94 these conditions has been established, such differences have not been studied with
95 regard to HELLP syndrome.

96 Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–
97 15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the
98 proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The
99 prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18)
100 and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in
101 high income countries, the association between maternal pre-pregnancy body-mass-
102 index (BMI) and HELLP syndrome has not been adequately assessed in a large
103 population-based study to date.

104 We carried out a population-based, retrospective cohort study to examine the
105 association between maternal pre-pregnancy BMI and HELLP syndrome and to assess
106 differences in this association in early- vs late-onset HELLP syndrome. We

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

107 hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this
108 relationship may be different in early- compared with late-onset disease. In additional
109 analyses, we examined other risk factors for HELLP syndrome in terms of their
110 association with early- vs late-onset HELLP syndrome.

111 **Materials and Methods**

112 *Data sources and study population*

113 The study included all live births and stillbirths at ≥ 20 weeks' gestation in British
114 Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from
115 the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes
116 information on >99% of births in BC, with detailed data on maternal demographic
117 characteristics, prenatal care, pregnancy complications, labor and delivery
118 characteristics and neonatal outcomes. Each record, abstracted from medical charts (or
119 midwives' notes), includes up to 25 International Classification of Diseases, 10th Edition,
120 Canadian version (ICD-10-CA) codes for diagnoses related to the delivery
121 hospitalization. Chart abstraction is standardized and conducted by trained personnel,

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 122 and data quality is routinely assessed. Prior validation studies showed high accuracy of
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9 123 collected information on labor and delivery.(21)

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13 124 *Pre-pregnancy BMI and HELLP syndrome*

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17 125 Pre-pregnancy weight and height were based on maternal self-report or health care

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20 126 provider assessment at ≤ 11 weeks' gestation.(22) BMI was classified as follows (in

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24 127 kg/m^2): underweight (< 18.5), normal ($18.5-24.9$), overweight ($25.0-29.9$), and obese

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27 128 (≥ 30.0).⁽²³⁾ The primary outcome of this study was a physician diagnosis of HELLP

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31 129 syndrome documented in the medical chart, and abstracted and recorded in the

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34 130 BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee

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38 131 classification criteria, namely lactate dehydrogenase ≥ 600 IU/l, liver transaminases

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41 132 (aspartate aminotransferase and alanine aminotransferase) elevated more than twice

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45 133 the upper limit of normal, and a platelet count $< 100,000/\mu\text{l}$ ($109/\text{l}$).⁽²⁴⁾ Early- and late-

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48 134 onset HELLP syndrome were defined as HELLP syndrome with delivery at < 34 weeks

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52 135 and ≥ 34 weeks' gestation, respectively. Early pregnancy ultrasound was used to

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

ascertain gestational age, and the last menstrual period estimate of gestational age was used for those without early pregnancy ultrasound information.

Covariates

In addition to BMI, we examined the association between maternal age, nulliparity, pre-existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as potential confounders; all these factors are known to be associated with HELLP syndrome.⁽²⁵⁾ Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic conditions and pregnancy complications were identified using ICD-10 codes or data fields abstracted from medical charts to the BCPDR (Table A.1).

Statistical analyses

The rates of HELLP syndrome per 1000 deliveries were compared between women in each BMI category. Complete case analyses were performed for individuals with known

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 151 BMI. The association between pre-pregnancy BMI and HELLP syndrome was first
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9 152 expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained
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12 153 from a Cox model without adjustment for other risk factors.
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15 154 Gestational age-specific rates of HELLP syndrome were compared between
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19 155 women in the various BMI categories, using undelivered pregnancies at each
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22 156 gestational week as the denominator. These rates were plotted, and splines with 95%
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26 157 confidence intervals were fitted by the generalized additive model (“gam”) smoothing
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29 158 method. Cox models with interaction terms between pre-pregnancy BMI categories and
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33 159 gestational age at HELLP onset (<34 vs ≥34 weeks’ gestation) were used to obtain
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36 160 crude HRs and 95% Confidence Intervals (CIs). This analysis was carried out to assess
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40 161 whether gestational age at onset modified the association between BMI and HELLP
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44 162 syndrome.
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47 163 In multivariable analyses, Cox models were also used to adjust for covariates
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50 164 (listed above) and to also examine their associations with early- vs late-onset of HELLP
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54 165 syndrome using interaction terms. We did not assess early- vs late-onset of HELLP
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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 166 syndrome interactions with risk factors including alcohol use and prior adverse birth
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9 167 outcomes due to a low number of women with HELLP syndrome in these categories,
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12 168 but adjusted for them in the model as potential confounders.
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16 169 Sensitivity analyses included multiple imputations for missing BMI values based
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19 170 on a multiple imputation procedure using SAS statistical software (PROC MI).(26)
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23 171 Variables included in the imputation were those also included in the regression
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26 172 analyses. Ten imputed datasets were created, with the final results obtained using
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30 173 Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were
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33 174 compared with the primary analyses.
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37 175 All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
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40 176 NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British
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44 177 Columbia/Children's and Women's Hospital and Health Centre of British Columbia
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47 178 Research Ethics Board (#H20-03985).
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51 179 ***Patient and Public Involvement***
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

180 Neither patients nor the public were involved in the design, or conduct, or reporting, or
181 dissemination plans of our research. We used only de-identified information and the
182 need for patient's consent was waived.

184 Results

185 *Study population*

186 Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,
187 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational
188 age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The
189 study population for the primary analyses included 391,941 pregnancies, after exclusion
190 of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP
191 syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

192 The proportion of women who were in underweight, normal BMI, overweight and
193 obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively.

194 Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 195 (stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational

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8 196 diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women

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12 197 with overweight and obesity compared with women with normal BMI (Table 1).

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15 198 Nulliparity and ultrasound diagnosed fetal growth restriction were observed more

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18 199 frequently in the underweight group. Substance use and smoking during pregnancy

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21 200 were more frequent in underweight, overweight, and obese groups compared with

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24 201 women with normal BMI.

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33 203 ***Unadjusted analyses for pre-pregnancy BMI***

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36 204 The rates of HELLP syndrome in women in underweight, normal, overweight, and

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39 205 obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table

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42 206 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and

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45 207 obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),

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48 208 respectively, compared with women who had normal BMI (Table A.2).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

209 The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2
210 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,
211 respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks
212 (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older
213 maternal age (≥ 35), pre-existing diabetes, chronic hypertension, multiple gestation,
214 bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance
215 use and smoking were higher among women with early-onset vs. late-onset HELLP
216 syndrome. Frequencies of underweight, younger maternal age (< 25 years), nulliparity,
217 IVF conception, and alcohol use were higher among women with late-onset HELLP
218 syndrome (Table A.3).

219 The rates of late-onset HELLP syndrome were higher than early-onset HELLP
220 syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous
221 women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal
222 death, IVF conception, multiple gestation, alcohol use and substance use also had
223 higher rates of late-onset than early-onset HELLP syndrome. Women with multiple

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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12 226 Differences in gestational age-specific incidence rates of HELLP syndrome by
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16 227 BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-
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19 228 age specific rates).

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23 229 Gestational age-specific rates of HELLP syndrome increased over the course of
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26 230 pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women
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29 231 with pre-pregnancy BMI below or above normal values but not among those with normal
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33 232 BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP
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36 233 syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and
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40 234 2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These
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44 235 HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP
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47 236 syndrome, respectively (Table A.2).

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54 238 ***Adjusted analyses***

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 239 The associations did not change substantially after adjusting for other risk factors (Table
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9 240 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on
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12 241 HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly
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15 242 associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP
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19 243 syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).

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23 244 Adjusted hazard ratios (AHR) for each risk factor calculated separately for early-
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26 245 vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly
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29 246 associated with HELLP syndrome included overweight, obesity, advanced maternal age
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33 247 (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation,
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36 248 and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse
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40 249 association with HELLP syndrome. IVF conception was a risk factor for late-onset but
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44 250 not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
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47 251 bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
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51 252 syndrome. Obesity ($p=0.025$), chronic hypertension ($p=0.041$), multiple gestation
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54 253 ($p=0.001$), bleeding before 20 weeks ($p=0.008$) and antepartum bleeding/hemorrhage
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

254 (p=0.011) differed significantly in their associations with early versus late-onset HELLP
255 syndrome (p-values for interaction).

256 *Sensitivity analyses*

257 Women with missing BMI were not substantially different from women with known BMI
258 (Table A.5); and the results were not appreciably changed after the analyses were
259 repeated using imputed BMI values (Table A.6).

261 Discussion

262 *Main findings*

263 To our knowledge, this is the largest contemporary study examining the association
264 between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
265 disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
266 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
267 lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
268 were at elevated risk for developing HELLP syndrome. Obesity was more strongly

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

269 associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
270 study showed that chronic hypertension, bleeding before 20 weeks' gestation and
271 antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP
272 syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP
273 syndrome.

274 *Interpretation in the context of scientific literature*

275 The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the
276 previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-
277 2016.(25) Prior studies describing the association between pre-pregnancy obesity and
278 HELLP syndrome are sparse and results vary. In a retrospective cohort study from a
279 single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal
280 weight was not associated with HELLP syndrome.(29) Similarly, a case-control study
281 (n= 129 cases and 476 controls) found no association between obesity and HELLP
282 syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases
283 and 601 controls) showed that pre-pregnancy BMI was associated with PE but not

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 284 HELLP syndrome and suggested that PE and HELLP may have different
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9 285 pathophysiology.(12) In contrast, a population-based cohort study from Norway
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12 286 (n=418,897) found that pre-pregnancy BMI $\geq 30\text{kg/m}^2$ was associated with HELLP
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16 287 syndrome in the first but not the second pregnancy.(9) However, in that study, only 25%
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19 288 of women with a first pregnancy and 30% of women with their second pregnancy had
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23 289 information on BMI. More recently, a population-based study from Canada
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26 290 (n=1,078,323) showed that obesity documented in medical charts was a risk factor for
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30 291 HELLP syndrome,(31) however, obesity rates were underestimated and information on
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34 292 BMI was not available, precluding more detailed analyses.

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36 293 While PE is typically recognized as early- vs late-onset disease (before vs ≥ 34
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40 294 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A
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44 295 prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is
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47 296 a stronger risk factor for late-onset PE than early-onset PE.(15) That study also
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51 297 demonstrated a correlation between increased prevalence of maternal obesity in
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54 298 parallel with late-onset PE during the 18-year period, while the incidence of early-onset

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 299 PE stayed relatively constant.(15) In contrast, our study shows a stronger association
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9 300 between overweight/obesity and early-onset HELLP syndrome compared with late-
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12 301 onset HELLP syndrome. This suggests varying pathophysiological pathways between
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15 302 PE and HELLP syndrome or additional obesity-related pathophysiology associated with
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19 303 PE that leads to liver damage at earlier gestation, for instance, obesity-associated
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22 304 steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age
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26 305 cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
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29 306 However, our data suggest an increase in gestational age-specific rates after 28 weeks'
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33 307 gestation in women with obesity and after 30 weeks' gestation in women without
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37 308 obesity. A previous study showed a high proportion of HELLP syndrome cases
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40 309 occurring between 27 and 37 weeks,(33) which indicates potential dissimilarities with
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44 310 early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk
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47 311 factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-
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51 312 onset disease. It is worth mentioning that the known inverse association between

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 313 smoking and PE(6) was also observed in HELLP syndrome in our study, and this

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9 314 warrants further investigation.

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12 315 *Clinical and research implications*

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15 316 Our findings show that increases in gestational age-specific rates of HELLP syndrome

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19 317 vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in

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23 318 women who were in the underweight, overweight and obese categories, but continued

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26 319 increasing in women with normal BMI. This could be due to higher rates of medically

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30 320 indicated early-term deliveries in groups with low or high BMI, which has been shown to

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33 321 reduce maternal morbidity compared with expectant management.(34) It is possible that

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37 322 women whose pre-pregnancy BMI was below and above normal range were more likely

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40 323 to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and

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44 324 therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal

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47 325 and infant outcomes. However, further research is needed to confirm this hypothesis. In

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50 326 addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks'

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54 327 gestation and antepartum bleeding/hemorrhage were more strongly associated with

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

328 early- onset HELLP syndrome, while multiple gestation was more strongly associated
329 with late-onset HELLP syndrome. The association between bleeding at <20 weeks
330 gestation and early-onset HELLP syndrome is novel. Such bleeding can be caused by
331 abnormal placental conditions (e.g., abnormal implantation and associated bleeding),
332 which may play a role in the development of HELLP syndrome. These findings are
333 exploratory and require confirmation by other studies. However, they raise the intriguing
334 possibility that determinants of HELLP syndrome (such as antepartum bleeding) have
335 different associations with early and late onset HELLP syndrome depending on whether
336 they occur at <20 weeks or at ≥ 20 weeks' gestation. In our study, the association
337 between antepartum bleeding at ≥ 20 weeks' gestation and HELLP syndrome (which
338 could have been explained as being a consequence of HELLP syndrome causing
339 placental abruption) was not significant in adjusted models.

340 ***Strengths and limitations***

341 The strengths of this study include its population-based design coupled with detailed
342 information about demographic, behavioural and clinical factors that allowed for robust

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 343 adjustment for possible confounding. We had a large enough sample to provide precise
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9 344 estimates for associations with HELLP syndrome, a rare outcome.

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12 345 This study also has several limitations. First, we did not have detailed information
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16 346 on laboratory values important for the diagnosis of HELLP syndrome and therefore we
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19 347 were not able to estimate the severity of HELLP. We assumed that the diagnosis of
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23 348 HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal
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26 349 condition. However, in milder cases, expectant management with close observation
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30 350 may have led to a delay between the diagnosis and delivery, especially at very preterm
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33 351 gestation. As a result, incidence of early-onset HELLP syndrome may have been
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37 352 underestimated in our study. However, we do not expect a large inaccuracy in this
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40 353 regard because HELLP syndrome is considered a potentially life-threatening condition
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44 354 and delivery is typically not delayed. Second, we did not have information about
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47 355 race/ethnicity, socio-economic status (SES) and prior history of pregnancy with
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51 356 PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding
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54 357 in the assessments of the relation between BMI and HELLP syndrome. However, we
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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 358 adjusted for several possible confounders and did not observe changes in the
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9 359 association between BMI and HELLP syndrome, suggesting that our results are robust.

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12 360 Third, pre-pregnancy BMI was largely self-reported, which may have led to some
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15 361 misclassification. Several validation studies have shown relatively good accuracy of
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19 362 self-reported weight and height for epidemiological studies,(35–37) suggesting that a
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23 363 large misclassification bias is unlikely. A systematic review of BMI self-report
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26 364 misclassification showed minimal influence on associations between BMI and
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30 365 pregnancy outcomes.(38)

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33 366 Approximately 25% of women had missing information about BMI. These women
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37 367 were relatively similar to those with known BMI and sensitivity analyses using imputed
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40 368 BMI values yielded results almost identical to the main analyses. Lastly, the analyses
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44 369 examining differences between early- and late-onset HELLP and risk factors other than
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47 370 BMI were exploratory, and further studies are required to confirm our findings.

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54 372 ***Conclusions***

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 373 Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk
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9 374 factor for HELLP syndrome. However, contrary to the documented association between
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12 375 BMI and PE, with obesity being associated more strongly with late-onset than early-
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16 376 onset PE, our study showed that obesity was more strongly associated with early-onset
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19 377 than with late-onset HELLP syndrome. This suggests potentially different underlying
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23 378 pathophysiology for the various hypertensive disorders of pregnancy. Our findings can
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26 379 help maternity care providers with regard to pre-pregnancy counselling. Clinicians can
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30 380 better identify women who may benefit from obstetric intervention, as the risk of HELLP
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33 381 increases at late pre-term gestation in all women and continues to increase at term and
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37 382 post-term gestation in women with normal pre-pregnancy BMI. More research on the
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40 383 gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the
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44 384 underlying causes of HELLP syndrome.

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 386 **Disclosure**

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9 387 The authors report no conflict of interest.

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12 388 **Disclaimer**

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16 389 All inferences, opinions, and conclusions drawn in this publication are those of the

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20 390 authors, and do not reflect the opinions or policies of Perinatal Services BC.

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24 391 **Author Statement/Contribution to Authorship**

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28 392 LW and SL were involved in the conception, planning, carrying out and analyzing data

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32 393 of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.

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35 394 LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ,

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39 395 NR.

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43 396 **Acknowledgement**

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48
49
50 398 to the BCPDR database.

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53 399 **Funding statement**

1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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6
7
8
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11
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13
14
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16
17
18
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23 405 sources were not involved in study design, data collection, analysis, and interpretation,
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26 406 writing of the manuscript, and/or decision to submit the article for publication.
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33 408 **Competing interests statement**

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36 409 The authors report no conflict of interest.
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40 410 **Data Sharing Statement**

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43 411 Data may be obtained from a third party and are not publicly available.
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47 412 **Ethics Approval Statement**
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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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5 413 Ethics approval was obtained from the University of British Columbia/Children's and

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9 414 Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-

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1 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

549 **Tables**550 **Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-**
551 **mass-index; British Columbia, 2008/09-2019/20^a**

	Underweight	Normal BMI	Overweight	Obese
	n = 22,392	n = 231,517	n = 83,864	n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception ^b	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets ^d	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction ^c	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery				
(weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

552 ^aData shown as n(%)

553 ^bIVF = in vitro fertilization

554 ^cUltrasound diagnosed intra-uterine growth restriction (IUGR)

555 ^dInformation on cell numbers <5 was suppressed due to confidentiality reasons.

556 **Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing**
 557 **pregnancies by maternal demographic and clinical characteristics; British Columbia,**
 558 **2008/09-2019/20**

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death ^a	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception ^b	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use ^a	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

559 ^aInformation on cell numbers <5 was suppressed due to confidentiality reasons. Other
 560 numbers were suppressed if needed to avoid back-calculation from the total

561 ^bIVF = in vitro fertilization

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

563 **Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with**
 564 **95% confidence intervals; British Columbia, 2008/09-2019/20**

	Overall AHR (95% CI) ^a	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P- value ^b
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
≥ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death ^c	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception ^d	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06- 16.87)	8.31 (5.59- 12.35)	17.81 (13.89- 22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (≥ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use ^e	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

565 ^aAHR = adjusted hazard ratio, with 95% confidence interval in parentheses, were obtained from
 566 the Cox model that included all variables in the table.

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5 567 ^bp-value for interaction with early- vs late-onset HELLP syndrome.

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7 568 ^cN/A = not applicable. We did not examine differences by early- vs late-onset for prior
8 569 stillbirth/neonatal death or alcohol use due to small sample size.

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10 570 ^dIVF = in vitro fertilization
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36 578 **Figure 1.** Gestational-age specific rates of HELLP syndrome for each BMI category
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39 579 (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were
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42 580 combined. Splines with 95% confidence intervals were fitted by the generalized additive
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46 581 model (“gam”) smoothing method.
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53 583 **Supplemental Figure 1.** Flowchart of study sample selection.
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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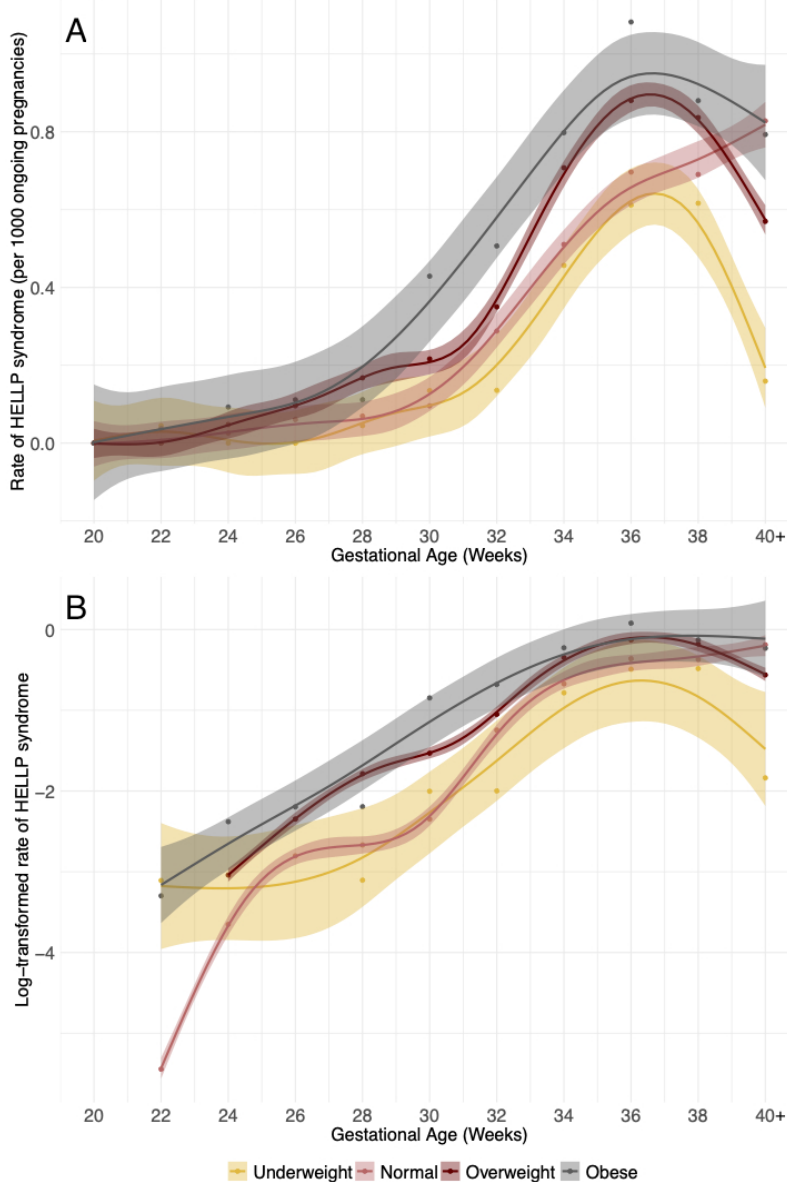
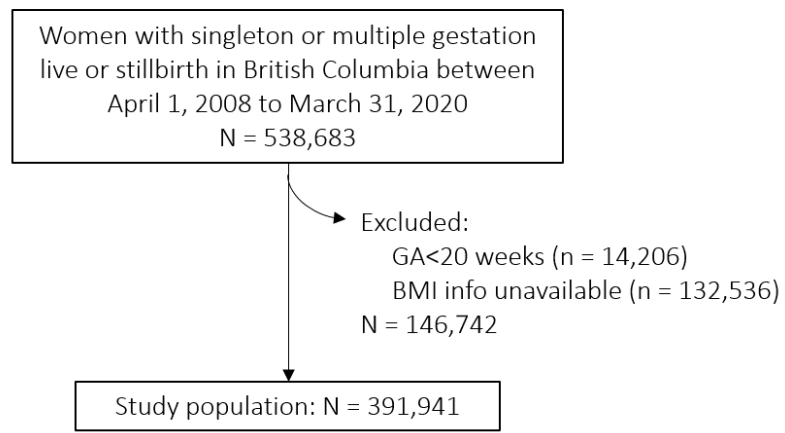


Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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Supplemental Figure 1. Flowchart of study sample selection.

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Supplementary tables

Supplemental Table 1. Definitions and sources of variables

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used; or 'E10','E11', 'O245','O246','O247'	ICD-10
Chronic hypertension	'O10','O11'	ICD-10
Prior stillbirth	Mother had at least one prior live born infant, who died within the first 28 days of life.	BCPDR
/neonatal death	Mother had at least one prior stillbirth or intrauterine death documented.	
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPDR
Multiple gestation	The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABORS.	BCPDR

Antepartum bleeding		
< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	BCPDR
Antepartum bleeding or hemorrhage ≥ 20 weeks	Mother had any antepartum hemorrhage or bleeding in pregnancy ≥ 20 weeks gestation, including bleeding from cervical polyps.	BCPDR
Intrauterine Growth Restriction ^a	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.	BCPDR
Gestational Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	BCPDR
Gestational Diabetes	Gestational diabetes, insulin dependent. Gestational diabetes, non-insulin dependent.	BCPDR
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother’s use of alcohol as a risk factor in this pregnancy.	BCPDR

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	Mother used any of the following substances at any time during the current pregnancy:	
Substance use	heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
HELLP syndrome	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low platelet count)	BCPDR

^aUltrasound diagnosed intra-uterine growth restriction (IUGR)

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Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and hazard ratios with 95% confidence intervals

	Underweight	Normal BMI	Overweight	Obese
<i>All pregnancies</i>				
N cases (rate per thousand) ^a	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR ^b	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
<i>Early-onset HELLP (< 34 wks)</i>				
N cases (rate per thousand) ^a	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR ^b	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)
<i>Late-onset HELLP (≥ 34 wks)</i>				
N cases (rate per thousand) ^a	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR ^b	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	1.42 (1.17-1.71)

^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34 weeks gestation (late-onset HELLP).

^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs late-onset HELLP syndrome; British Columbia, 2008/09-2019/20^a

	Early-onset HELLP	Late-onset HELLP
	n =275	n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)
Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)

Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death ^b	<5 (<1.8)	<5 (<0.5)
IVF conception ^c	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use ^b	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

^aData shown as n(%)

^bInformation on cell numbers <5 was suppressed due to confidentiality reasons.

^cIVF = in vitro fertilization

Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per 1000 ongoing pregnancies)^a

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	<5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	<5/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)
32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
34-35	10/21902 (0.46)	116/227212 (0.51)	58/81998 (0.71)	42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	55/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	36/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

^aInformation on cell numbers <5 was suppressed due to confidentiality reasons.

Supplemental Table 5. Demographic and clinical characteristics of women missing pre-pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20^a

	BMI not missing	BMI missing
	n = 391,941	n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception ^b	11549 (3.0)	3877 (2.9)
Multiple gestation		
Twins	5806 (1.5)	2478 (1.9)

1			
2			
3	Triplets/Quadruplets	82 (0)	27 (0)
4			
5			
6	Antepartum bleeding/hemorrhage		
7			
8	< 20 weeks	7337 (1.9)	1813 (1.4)
9			
10	≥ 20 weeks	5659 (1.4)	1496 (1.1)
11			
12			
13	Intrauterine Growth Restriction ^c	8857 (2.3)	2471 (1.9)
14			
15			
16	Gestational Hypertension	21124 (5.4)	6623 (5.0)
17			
18	Gestational Diabetes	44172 (11.3)	13248 (10.0)
19			
20			
21	Proteinuria	21124 (5.4)	6623 (5.0)
22			
23	Alcohol use	4162 (1.1)	1845 (1.4)
24			
25			
26	Substance use	15701 (4.0)	6758 (5.1)
27			
28	Smoking	26401 (6.7)	10435 (7.9)
29			
30			
31	Second-hand smoke	26319 (6.7)	7565 (5.7)
32			

^aData shown as n(%)

^bIVF = in vitro fertilization

^cUltrasound diagnosed intra-uterine growth restriction (IUGR)

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Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data for missing values of BMI

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand) ^a	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR ^b	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) ^a	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)
Adjusted HR ^b	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2.08)

^aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

^bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title page	“Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.”
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	31	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 - 147
		(b) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 - 147
		(c) Explain how missing data were addressed	6-7	Lines 123 - 147
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	N/A	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-29, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(b) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-23	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-23	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.