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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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Keywords:	Obesity, EPIDEMIOLOGY, OBSTETRICS

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7 8	2	hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-
9 10		
10	3	based retrospective cohort study.
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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18 19 20	21	Address: 950 W 28 <sup>th</sup> Ave, Vancouver, BC V5Z 4H4
21 22 23 24	22	Work: 604-875-3015; Cell: 778-513-1648; Email: liqing.wang@bcchr.ca
25 26	23	
27 28 29	24	Abstract
30 31 32 33	25	Background: Obesity increases risk of pre-eclampsia, but the association with
34 35 36	26	hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
37 38 39	27	understudied.
40 41 42 43	28	<b>Objective:</b> To examine the association between pre-pregnancy body-mass-index (BMI)
44 45 46	29	and HELLP syndrome, including early- vs. late-onset disease.
47 48 49 50	30	Study Design: A retrospective cohort study, population-based data.
51 52 53	31	Setting: British Columbia (BC), Canada, 2008/09-2019/20.
54 55 56 57	32	<b>Population:</b> All pregnancies resulting in live births or stillbirths at $\geq$ 20 weeks' gestation.
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Pre-pregnancy BMI and early- and late-onset HELLP syndrome **Methods:** BMI categories (kg/m<sup>2</sup>) 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 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	47	gestation and antepartum) also showed differing AHRs between early- vs. late-onset
8 9 10	48	HELLP.
11 12 13 14	49	Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the
15 16 17	50	association is stronger with early-onset HELLP syndrome. Associations with early- and
18 19 20 21	51	late-onset HELLP syndrome differed for some risk factors, suggesting possible
22 23 24	52	differences in etiologic mechanisms.
25 26 27 28	53	Strengths and limitations of this study
29 30 31	54	We were able to describe gestational age-specific incidence of HELLP
32 33 34 35	55	syndrome, which requires population data on all pregnancies.
36 37 38	56	<ul> <li>Population-based design coupled with detailed information about demographic,</li> </ul>
39 40 41 42	57	behavioural and clinical factors that allowed for robust adjustment for possible
43 44 45	58	confounding.
46 47 48 49	59	• We did not have detailed information on laboratory values used for the diagnosis
50 51 52	60	of HELLP syndrome and therefore we were not able to estimate the severity of
53 54 55 56	61	HELLP.
57 58 59		For near review only - http://bmionen.hmi.com/site/about/quidalinas.yhtml
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1 2 3		5 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	62	• We did not have information about race/ethnicity, socio-economic status (SES)
8 9 10	63	and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
11 12 13 14	64	• Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had
15 16 17	65	missing information about BMI, we used multiple imputation methods to address
18 19 20 21	66	this limitation.
22 23 24	67	
25 26 27 28	68	Funding statement
29 30 31	69	This study was funded by the Canadian Institutes for Health Research (CIHR) and the
32 33 34	70	SickKids Foundation (CIHR SKF – 154852). LW receives support from a CIHR Doctoral
35 36 37 38	71	Fellowship, KSJ is supported by an Investigator award from the BC Children's Hospital
39 40 41	72	Research Institute, Canada, NR is supported by a grant from the Swedish Research
42 43 44 45	73	Council for Health, Working Life and Welfare (grant no. 2019-00041). The funding
46 47 48	74	sources were not involved in study design, data collection, analysis, and interpretation,
49 50 51 52	75	writing of the manuscript, and/or decision to submit the article for publication.
53 54 55 56	76	Competing interests statement
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	77	The authors report no conflict of interest.	
8 9 10	78	Key words	
11 12 13 14	79	Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity,	
15 16 17	80	pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP	
18 19 20 21	81	syndrome.	
22 23 24	82	Word count: 3036	
25 26 27 28	83		
29 30 31	84		
32 33 34	85		
35 36 37 38	86		
39 40 41	87		
42 43 44 45	88		
46 47 48	89		
49 50 51 52	90		
53 54 55 56	91		
57 58			
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	92	
8 9 10 11	93	
12 13 14	94	
15 16 17	95	
18 19 20	96	
21 22 23 24	97	Introduction
25 26 27 28	98	Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the
29 30 31	99	leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies
32 33 34 35	100	worldwide <sup>1,2</sup> and accounting for up to 14% of maternal deaths. <sup>3</sup> Early-onset PE at <34
36 37 38	101	weeks' gestation is often associated with placental insufficiency whereas late-onset PE
39 40 41 42	102	is often associated with pre-existing maternal health conditions such as metabolic
43 44 45	103	syndrome and obesity. <sup>4</sup> Early- vs late-onset PE differ in some risk factors, clinical
46 47 48 49	104	management and rates of adverse perinatal outcomes. <sup>5,6</sup> Hemolysis, elevated liver
50 51 52	105	enzymes, and low platelets (HELLP) syndrome occurs in 0.2-0.8% of pregnancies <sup>7–9</sup>
53 54 55 56 57	106	and 10-20% of cases of severe PE. <sup>10</sup> Although HELLP syndrome has been
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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	107	distinguished from PE as a separate disease, <sup>11</sup> it is still widely regarded as a form of
8 9 10	108	severe PE. <sup>9</sup> While the distinction between early- and late-onset PE and the differences
12 13 14	109	in the association with pre-pregnancy obesity has been established, these differences
15 16 17	110	have not been studied in HELLP syndrome.
19 20 21	111	Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia. <sup>12–15</sup> To
22 23 24	112	date, the world prevalence of obesity has nearly tripled since 1975 <sup>16</sup> and the proportion
25 26 27 28	113	of pregnant women with obesity ranges from 1.8% to 25.3% globally. <sup>17</sup> The prevalence
29 30 31	114	of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada <sup>18</sup> and 29.0% in
33 34 35	115	2019 in the United States. <sup>19</sup> Despite the large increases in obesity in high income
36 37 38 20	116	countries, the association between maternal pre-pregnancy body-mass-index (BMI) and
40 41 42	117	HELLP syndrome has not been adequately assessed in a large population-based study
43 44 45	118	to date.
40 47 48 49	119	We carried out a population-based, retrospective cohort study to examine the
50 51 52	120	association between maternal pre-pregnancy BMI and HELLP syndrome and to assess
53 54 55 56 57 58	121	differences in this association in early- vs late-onset HELLP syndrome. We
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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	-
5 5 7	122	hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this	
8 9 10	123	relationship may be different in early- compared with late-onset disease. In additional	
11 12 13 14	124	analyses, we examined other risk factors for HELLP syndrome in terms of their	
15 16 17	125	association with early- vs late-onset HELLP syndrome.	
18 19 20	126	Materials and Methods	
22 23 24	127	Data sources and study population	
25 26 27	128	The study included all live births and stillbirths at ≥20 weeks' gestation in British	
29 30 31	129	Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from	
32 33 34	130	the British Columbia Perinatal Database Registry (BCPDR).20 The BCPDR includes	
36 37 38	131	information on >99% of births in BC, with detailed data on maternal demographic	
39 40 41	132	characteristics, prenatal care, pregnancy complications, labor and delivery	
42 43 44 45	133	characteristics and neonatal outcomes. Each record, abstracted from medical charts (or	
46 47 48	134	midwives' notes), includes also up to 25 ICD-10-CA (International Classification of	
49 50 51 52	135	Diseases, 10 <sup>th</sup> Edition, Canada) codes for diagnoses related to delivery hospitalization	
53 54 55 56 57 58	136	and following hospital transfers if applicable. Chart abstraction is standardized and	
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1 2 2		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
3 4 5	127	conducted by trained personnel, and data quality is routinely assessed. Prior validation
6 7	137	conducted by trained personnel, and data quality is routinely assessed. Filor validation
8 9 10 11 12	138	studies showed high accuracy of collected information on labor and delivery. <sup>21</sup>
13 14 15	139	Pre-pregnancy BMI and HELLP syndrome
16 17 18 19	140	Pre-pregnancy weight and height were based on maternal self-report or health care
20 21 22 23	141	provider assessment at ≤11 weeks' gestation. <sup>22</sup> Body-mass-index (BMI) was classified
24 25 26	142	as follows (in kg/m <sup>2</sup> ): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9),
27 28 29 30	143	and obese (≥30.0). <sup>23</sup> The primary outcome of this study was a physician diagnosis of
31 32 33	144	HELLP syndrome in the medical chart, abstracted and recorded in the BCPDR. In
34 35 36 27	145	Canada, HELLP syndrome is typically diagnosed by the following criteria: LDH ≥600
38 39 40	146	IU/I, liver transaminases (AST and ALT) elevated more than twice the upper limit of
41 42 43	147	normal, and a platelet count <100,000/µl ( $10^{9}$ /l). Early- and late-onset HELLP syndrome
44 45 46 47	148	were defined as HELLP syndrome with delivery at <34 weeks and ≥34 weeks'
48 49 50	149	gestation, respectively. Early pregnancy ultrasound was used to ascertain gestational
52 53 54	150	age, and last menstrual period was used for those with missing early pregnancy
55 56 57 58	151	ultrasound.
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1 2 3 4		11 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	152	Covariates
8 9 10 11	153	In addition to BMI, we examined the association between maternal age, nulliparity, pre-
12 13 14	154	existing diabetes, chronic hypertension, <i>in vitro</i> fertilization (IVF) conception, multiple
15 16 17 18	155	gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance
19 20 21	156	use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol
22 23 24	157	use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as
25 26 27 28	158	potential confounders; all these factors are known to be associated with HELLP
29 30 31	159	syndrome. <sup>24</sup> Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic
32 33 34 35	160	conditions and pregnancy complications were identified using ICD-10 codes or data
36 37 38	161	fields abstracted from medical charts to the BCPDR (Table A.1).
39 40 41 42	162	Statistical analyses
43 44 45	163	The rates of HELLP syndrome per 1000 deliveries were compared between women in
46 47 48 49	164	each BMI category. Complete case analyses were performed for individuals with known
50 51 52 53 54 55 56 57 58	165	BMI. The association between pre-pregnancy BMI and HELLP syndrome was
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	166	expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained
8 9 10	167	from a Cox model without adjustment for other risk factors.
11 12 13 14	168	Gestational age-specific rates of HELLP syndrome were compared between
15 16 17	169	women in the various BMI categories, using undelivered pregnancies at each
18 19 20 21	170	gestational week as the denominator. These rates were plotted, and splines with 95%
22 23 24	171	confidence intervals were fitted by the generalized additive model ("gam") smoothing
25 26 27 28	172	method. Cox models with interaction terms between pre-pregnancy BMI categories and
29 30 31	173	gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain
32 33 34 25	174	crude HRs and 95% CIs. This analysis was carried out to assess whether gestational
36 37 38	175	age at onset modified the association between BMI and HELLP syndrome.
39 40 41 42	176	In multivariable analyses, Cox models were also used to adjust for covariates
42 43 44 45	177	(listed above) and to also examine their associations with early- vs late-onset of HELLP
46 47 48	178	syndrome using interaction terms. We did not assess early- vs late-onset of HELLP
49 50 51 52	179	syndrome interactions with risk factors including alcohol use and prior adverse birth
53 54 55 56		
57 58 59		
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- Pre-pregnancy BMI and early- and late-onset HELLP syndrome outcomes due to a low number of women with HELLP in these categories, but adjusted for them in the model as potential confounders. Sensitivity analyses included multiple imputations for missing BMI values based on a multiple imputation procedure using SAS statistical software (PROC MI).<sup>25</sup>
  - Variables included in the imputation were those also included in the regression
  - analyses. Ten imputed datasets were created, with the final results obtained using
  - Rubin's rule.<sup>26</sup> All analyses were repeated with the imputed dataset and results were
  - compared with the primary analyses.
  - All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
  - NC) and R version 4.0.3.27 Ethics approval was obtained from the University of British
  - Columbia/Children's and Women's Hospital and Health Centre of British Columbia
  - Research Ethics Board (#H20-03985).
  - Patient and Public Involvement
  - Patients or the public WERE NOT involved in the design, or conduct, or reporting, or
  - dissemination plans of our research.

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	4
4 5 6 7	195		
8 9 10 11	196	Results	
12 13 14	197	Study population	
15 16 17 18	198	Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,	
19 20 21	199	2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational	
22 23 24 25	200	age or those with <20 weeks' gestation were excluded (n=14,206, 2.6%). The study	
26 27 28	201	population for the primary analyses included 391,941 pregnancies, after exclusion of	
29 30 31 32	202	women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP	
33 34 35	203	syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).	
36 37 38 39	204	The proportion of women who were in underweight, normal BMI, overweight and	
40 41 42	205	obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively	•
43 44 45 46	206	Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes	
47 48 49	207	(stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational	
50 51 52 53	208	diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women	
54 55 56 57 58	209	with overweight and obesity compared with women with normal BMI (Table 1).	
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	15
5 6 7	210	Nulliparity and ultrasound diagnosed fetal growth restriction were observed more	
8 9 10 11	211	frequently in the underweight group. Substance use and smoking during pregnancy	
12 13 14	212	were more frequent in underweight, overweight, and obese groups compared with	
15 16 17	213	women with normal BMI.	
18 19 20 21	214		
22 23 24 25	215	Unadjusted analyses for pre-pregnancy BMI	
26 27 28	216	The rates of HELLP syndrome in women in underweight, normal, overweight, and	
29 30 31	217	obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Tab	le
33 34 35	218	2). Overall, crude HRs for HELLP syndrome in women who were in the overweight an	d
36 37 38	219	obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),	
39 40 41 42	220	respectively, compared with women who had normal BMI (Table A.2).	
43 44 45	221	The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2	
46 47 48 49	222	(n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,	
50 51 52	223	respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weel	٢S
53 54 55 56 57 58 59	224	(75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older	

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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	225	maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation,
8 9 10	226	bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance
12 13 14	227	use and smoking were higher among women with early-onset vs. late-onset HELLP
15 16 17	228	syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity,
18 19 20 21	229	IVF conception, and alcohol use were higher among women with late-onset HELLP
22 23 24	230	syndrome (Table A.3).
25 26 27 28	231	The rates of late-onset HELLP syndrome were higher than early-onset HELLP
29 30 31	232	syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous
32 33 34 35	233	women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal
36 37 38	234	death, IVF conception, multiple gestation, alcohol use and substance use also had
39 40 41 42	235	higher rates of late-onset than early-onset HELLP syndrome. Women with multiple
43 44 45	236	gestation had highest rate of HELLP syndrome, followed by those with chronic
46 47 48 49 50 51 52 53 54	237	hypertension.
55 56 57 58 59		
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1 2 3		17 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	238	Differences in gestational age-specific incidence rates of HELLP syndrome by
8 9 10 11	239	BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-
12 13 14	240	age specific rates).
15 16 17	241	Gestational age-specific rates of HELLP syndrome increased over the course of
19 20 21	242	pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women
22 23 24	243	with pre-pregnancy BMI below or above normal values but not among those with normal
25 26 27 28	244	BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP
29 30 31	245	syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and
32 33 34 35	246	2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These
36 37 38	247	HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP
39 40 41 42	248	syndrome, respectively (Table A.2).
43 44 45	249	
46 47 48 49	250	Adjusted analyses
50 51 52	251	The associations did not change substantially after adjusting for other risk factors (Table
53 54 55 56 57	252	3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	253	HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly
8 9 10	254	associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP
11 12 13 14	255	syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).
15 16 17	256	Adjusted hazard ratios (AHR) for each risk factor calculated separately for early-
18 19 20 21	257	vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly
22 23 24	258	associated with HELLP syndrome included overweight, obesity, advanced maternal age
25 26 27 28	259	(≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation,
29 30 31	260	and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse
32 33 34	261	association with HELLP syndrome. IVF conception was a risk factor for late-onset but
36 37 38	262	not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
39 40 41	263	bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
42 43 44 45	264	syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation
46 47 48	265	(p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage
49 50 51 52	266	(p=0.011) differed significantly in their associations with early versus late-onset HELLP
53 54 55 56 57	267	syndrome (p-values for interaction).
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1		15
1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	268	Sensitivity analyses
8 9 10 11	269	Women with missing BMI were not substantially different from women with known BMI
12 13 14	270	(Table A.5); and the results were not appreciably changed after the analyses were
15 16 17	271	repeated using imputed BMI values (Table A.6).
18 19 20 21	272	
22 23 24	273	Discussion
25 26 27 28	274	Main findings
29 30 31	275	To our knowledge, this is the largest contemporary study examining the association
32 33 34 35	276	between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
36 37 38	277	disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
39 40 41 42	278	34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
43 44 45	279	lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
46 47 48 49	280	were at elevated risk for developing HELLP syndrome. Obesity was more strongly
50 51 52	281	associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
53 54 55 56 57	282	study showed that chronic hypertension, bleeding before 20 weeks' gestation and
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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
- 5 6 7	283	antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP
8 9 10 11	284	syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP
12 13 14	285	syndrome.
15 16 17	286	Interpretation in the context of scientific literature
19 20 21	287	The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the
22 23 24	288	previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-
25 26 27 28	289	2016. <sup>24</sup> Prior studies describing the association between pre-pregnancy obesity and
29 30 31	290	HELLP syndrome are sparse and results vary. In a retrospective cohort study from a
32 33 34 35	291	single tertiary hospital in the United States (n=434), Martin <i>et al.</i> found that maternal
36 37 38	292	weight was not associated with HELLP syndrome. <sup>28</sup> Similarly, a case-control study (n=
39 40 41 42	293	129 cases and 476 controls) found no association between obesity and HELLP
43 44 45	294	syndrome. <sup>29</sup> Furthermore, a retrospective case-control study (including n=687 cases
46 47 48 49	295	and 601 controls) showed that pre-pregnancy BMI was associated with PE but not
50 51 52	296	HELLP syndrome and suggested that PE and HELLP may have different
53 54 55 56 57 58	297	pathophysiology. <sup>12</sup> In contrast, a population-based cohort study from Norway
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		2 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	298	(n=418,897) found that pre-pregnancy BMI ≥30kg/m <sup>2</sup> was associated with HELLP
8 9 10	299	syndrome in the first but not the second pregnancy.9 However, in that study, only 25%
11 12 13 14	300	of women with a first pregnancy and 30% of women with their second pregnancy had
15 16 17	301	information on BMI. More recently, a population-based study from Canada
18 19 20 21	302	(n=1,078,323) showed that obesity documented in medical charts was a risk factor for
22 23 24	303	HELLP syndrome, <sup>30</sup> however, obesity rates were underestimated and information on
25 26 27 28	304	BMI was not available, precluding more detailed analyses.
29 30 31	305	While PE is typically recognized as early- vs late-onset disease (before vs $\geq$ 34
32 33 34 35	306	weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A
36 37 38	307	prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is
39 40 41 42	308	a stronger risk factor for late-onset PE than early-onset PE. <sup>15</sup> That study also
43 44 45	309	demonstrated a correlation between increased prevalence of maternal obesity in
46 47 48 49	310	parallel with late-onset PE during the 18-year period, while the incidence of early-onset
50 51 52	311	PE stayed relatively constant. <sup>15</sup> In contrast, our study shows a stronger association
53 54 55 56 57 58 59	312	between overweight/obesity and early-onset HELLP syndrome compared with late-

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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	313	onset HELLP syndrome. This suggests varying pathophysiological pathways between
8 9 10 11	314	PE and HELLP syndrome or additional obesity-related pathophysiology associated with
12 13 14	315	PE that leads to liver damage at earlier gestation, for instance, obesity-associated
15 16 17 18	316	steatosis and non-alcoholic fatty liver disease. <sup>31</sup> We chose the same gestational age
19 20 21	317	cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
22 23 24 25	318	However, our data suggest an increase in gestational age-specific rates after 28 weeks'
26 27 28	319	gestation in women with obesity and after 30 weeks' gestation in women without
29 30 31 32	320	obesity. A previous study showed a high proportion of HELLP syndrome cases
33 34 35	321	occurring between 27 and 37 weeks <sup>32</sup> which indicates potential dissimilarities with early-
36 37 38 39	322	vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk factor
40 41 42	323	for early-onset disease for both PE <sup>6</sup> and HELLP syndrome compared with late-onset
43 44 45 46	324	disease. It is worth mentioning that the known inverse association between smoking
47 48 49	325	and PE <sup>6</sup> was also observed in HELLP syndrome in our study, and this warrants further
50 51 52 53	326	investigations.
54 55 56 57 58	327	Clinical and research implications
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1		2	3
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	328	Our findings show that increases in gestational age-specific rates of HELLP syndrome	
8 9 10	329	vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in	
11 12 13 14	330	women who were in the underweight, overweight and obese categories, but continued	
15 16 17	331	increasing in women with normal BMI. This could be due to higher rates of medically	
18 19 20 21	332	indicated early-term deliveries in groups with low or high BMI, which has been shown to	)
22 23 24	333	reduce maternal morbidity compared with expectant management. <sup>33</sup> It is possible that	
25 26 27 28	334	women whose pre-pregnancy BMI was below and above normal range were more likely	1
29 30 31	335	to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and	
32 33 34 35	336	delivered at early term (37-38 weeks) to prevent adverse maternal and infant outcomes	·-
36 37 38	337	In addition to BMI, we also showed that chronic hypertension, bleeding before 20	
39 40 41 42	338	weeks' gestation and antepartum bleeding/hemorrhage were more strongly associated	
43 44 45	339	with early- onset HELLP syndrome, while multiple gestation was more strongly	
46 47 48 49	340	associated with late-onset HELLP syndrome. These findings suggest that risk factors for	۶r
50 51 52	341	HELLP syndrome have varied clinical relevance based on gestational age at onset of	
53 54 55 56 57 58	342	the disease.	

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	343	Strengths and limitations
8 9 10	344	The strengths of this study include its population-based design coupled with detailed
12 13 14	345	information about demographic, behavioural and clinical factors that allowed for robust
15 16 17	346	adjustment for possible confounding. We had a large enough sample to provide precise
19 20 21	347	estimates for associations with HELLP syndrome, a rare outcome.
22 23 24	348	This study also has several limitations. First, we did not have detailed information
25 26 27 28	349	on laboratory values important for the diagnosis of HELLP syndrome and therefore we
29 30 31	350	were not able to estimate the severity of HELLP. We assumed that the diagnosis of
32 33 34 35	351	HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal
36 37 38	352	condition. However, in milder cases, expectant management with close observation
39 40 41 42	353	may have led to a delay between the diagnosis and delivery, especially at very preterm
43 44 45	354	gestation. As a result, incidence of early-onset HELLP syndrome may have been
46 47 48 49	355	underestimated in our study. However, we do not expect a large inaccuracy in this
50 51 52	356	regard because HELLP syndrome is considered a potentially life-threatening condition
53 54 55 56 57 58	357	and delivery is typically not delayed. Second, we did not have information about
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	358	race/ethnicity, socio-economic status (SES) and prior history of pregnancy with	
8 9 10	359	PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding	
11 12 13 14	360	in the assessments of the relation between BMI and HELLP syndrome. However, we	
15 16 17	361	adjusted for several possible confounders and did not observe changes in the	
18 19 20 21	362	association between BMI and HELLP syndrome, suggesting that our results are robust	
22 23 24	363	Third, pre-pregnancy BMI was largely self-reported, which may have led to some	
25 26 27	364	misclassification. Several validation studies have shown relatively good accuracy of	
29 30 31	365	self-reported weight and height for epidemiological studies, <sup>34–36</sup> suggesting that a large	
32 33 34	366	misclassification bias is unlikely. A systematic review of BMI self-report	
35 36 37 38	367	misclassifications showed minimal influence on associations of BMI with pregnancy	
39 40 41	368	outcomes. <sup>37</sup>	
42 43 44 45	369	Approximately 25% of women had missing information about BMI. These women	า
46 47 48	370	were relatively similar to those with known BMI and sensitivity analyses using imputed	
49 50 51 52	371	BMI values yielded results almost identical to the main analyses. Lastly, the analyses	
53 54 55			
56 57 58 59			

1		26
2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	372	examining differences between early- and late-onset HELLP and risk factors other than
8 9 10 11	373	BMI were exploratory, and further studies are required to confirm our findings.
12 13 14	374	
15 16 17 18	375	Conclusions
19 20 21	376	Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk
22 23 24 25	377	factor for HELLP syndrome. However, contrary to the documented association between
26 27 28	378	BMI and PE, with obesity being associated more strongly with late-onset than early-
29 30 31 32	379	onset PE, our study showed that obesity was more strongly associated with early-onset
33 34 35	380	than with late-onset HELLP syndrome. This information suggests different underlying
36 37 38 20	381	pathophysiology of the various hypertensive disorders of pregnancy. Our findings can
40 41 42	382	help maternity care providers with regard to pre-pregnancy counselling. Clinicians can
43 44 45	383	better identify women who may benefit from obstetric intervention, as the risk of HELLP
40 47 48 49	384	increases at late pre-term gestation in all women and continues to increase at term and
50 51 52 53 54 55 56 57 58	385	post-term gestation in women with normal pre-pregnancy BMI. More research on the
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	386	gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the
, 8 9 10	387	underlying causes of HELLP syndrome.
11 12 13	388	
$\begin{array}{c} 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 59\end{array}$		for beer terien only
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	28
4 5 6 7	389	Disclosure	
, 8 9 10 11	390	The authors report no conflict of interest.	
12 13 14	391	Disclaimer	
15 16 17 18	392	All inferences, opinions, and conclusions drawn in this publication are those of the	
19 20 21 22	393	authors, and do not reflect the opinions or policies of Perinatal Services BC.	
23 24 25 26	394	Author Statement/Contribution to Authorship	
27 28 29 30	395	LW and SL were involved in the conception, planning, carrying out and analyzing data	l
31 32 33	396	of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.	
34 35 36 37	397	LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ	,
38 39 40 41	398	NR.	
42 43 44	399	Acknowledgement	
43 46 47 48	400	We thank the Women's Health Research Institute (WHRI) for providing us with access	;
49 50 51 52	401	to the BCPDR database.	
53 54 55 56 57 58	402		
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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	Pre-pregnancy BMI and ear	ly- and late-c	onset HELLP sy	ndrome		
528	Tables					
529 530	Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-					
		Underweigh	tNormal 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.	
	≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24	
	Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40	
	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 <sup>b</sup>	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 <sup>d</sup>	<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	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)	
	weeks)					
	Intrauterine Growth	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)	
	Restriction <sup>c</sup>	- (/	- (/	()	()	
	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.	

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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) 2970 (5.5) Substance use 1118 (5.0) 8099 (3.5) 3514 (4.2) 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) 387 (1.7) 28-33 3423 (1.5) 1473 (1.8) 1158 (2.1) 4680 (8.6) 34-36 6142 (7.3) 1620 (7.2) 15119 (6.5) 20076 209831 (90.6) 75017 (89.5) 47448 (87.6) 37-41 (89.7)≥ 42 207 (0.9) 2263 (1.0) 839 (1.0) 524 (1.0) 531 <sup>a</sup>Data shown as n(%) 532 <sup>b</sup>IVF = in vitro fertilization 533 <sup>c</sup>Ultrasound diagnosed intra-uterine growth restriction (IUGR) <sup>d</sup>Information on cell numbers <5 was suppressed due to confidentiality reasons. 534 Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing 535 pregnancies by maternal demographic and clinical characteristics; British Columbia, 536 537 2008/09-2019/20 Early-onset Late-onset HELLP HELLP Overall syndrome syndrome Pre-pregnancy BMI category 43 (1.9) Underweight 8 (0.4) 35 (1.6) 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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1 2		Pre-pregnancy BMI and early- and lat	e-onset HELLP syn	drome	40			
_ 3 ∡								
5		25-34	158 (0.6)	512 (2.1)	670 (2.7)			
7		≥ 35	87 (0.9)	232 (2.4)	319 (3.3)			
8 9		Nullipara	188 (1.0)	629 (3.4)	817 (4.3)			
10 11		Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)			
12 13		Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)			
14 15		Prior stillbirth /neonatal deatha	<5 (<1.0)	<5 (<1.0)	5 (1.3)			
16 17		IVF conception <sup>b</sup>	19 (1.6)	73 (6.7)	92 (8.0)			
17		Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)			
19 20		Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)			
21 22 23 24 25 26 27 28 29 30 31 32 33 24		Antepartum Bleeding/hemorrhage (≥ 20						
		weeks)	15 (2.7)	12 (2.5)	27 (4.8)			
		Alcohol use <sup>a</sup>	<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	<sup>a</sup> Information on cell numbers <5 was suppressed due to confidentiality reasons. Other						
	539	numbers were suppressed if needed to avoid back-calculation from the total						
34 35	540	<sup>b</sup> IVF = in vitro fertilization						
36 27	541							
37 38								
39 40								
41 42								
43 44								
45								
46 47								
48 49								
50 51								
52 52								
53 54								
55 56								
57 58								

#### 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

7 (0.33-1.38) 0. R 3 (1.22-2.18) 1. 4 (1.65-3.04) 1. 2 (0.62-1.38) 0.	.82 (0.58-1.16) ef .26 (1.07-1.49) .48 (1.23-1.80) .92 (0.74-1.15)	0.628 Ref 0.129 0.025 0.998
7 (0.33-1.38) 0. R 3 (1.22-2.18) 1. 4 (1.65-3.04) 1. 2 (0.62-1.38) 0.	.82 (0.58-1.16) ef .26 (1.07-1.49) .48 (1.23-1.80) .92 (0.74-1.15)	0.628 Ref 0.129 0.025
R 3 (1.22-2.18) 1. 4 (1.65-3.04) 1. 2 (0.62-1.38) 0. R	ef .26 (1.07-1.49) .48 (1.23-1.80) .92 (0.74-1.15)	Ref 0.129 0.025 0.998
3 (1.22-2.18) 1. 4 (1.65-3.04) 1. 2 (0.62-1.38) 0.	.26 (1.07-1.49) .48 (1.23-1.80) .92 (0.74-1.15)	0.129 0.025 0.998
4 (1.65-3.04) 1. 2 (0.62-1.38) 0.	.48 (1.23-1.80) .92 (0.74-1.15)	0.025
2 (0.62-1.38)   0.	.92 (0.74-1.15)	0.998
2 (0.62-1.38)  0.	.92 (0.74-1.15)	0.998
R		2.200
	ef	Ref
9 (1.06-1.83) 1.	.23 (1.05-1.45)	0.445
6 (1.97-3.33) 3.	.09 (2.63-3.63)	0.229
4 (0.71-3.81) 2.	.88 (1.66-5.00)	0.273
5 (3.62-9.79) 2.	.92 (1.83-4.66)	0.041
	/A	N/A
3 (0.50-1.41) 1.	.37 (1.04-1.80)	0.101
1 (5.59- 17 35) 22	7.81 (13.89- 2.83)	0.001
9 (1.05-3.39) 0.	.60 (0.32-1.12)	800.0
	07 (0 77 0 40)	0.044
	.37 (0.77-2.43)	0.011
5 (2.22-6.35) 1.	/Δ	N/A
5 (2.22-6.35) 1. N		0.166
5 (2.22-6.35) 1. N 8 (0.78-2.42) 0.	.84 (0.56-1.27)	
	N N	N/A 8 (0.78-2.42) 0.84 (0.56-1.27)

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
4 5	F 4 C	he value for interaction with early validate enact UEUD evadrome	
6	546	<sup>o</sup> p-value for interaction with early- vs late-onset HELLP syndrome.	
7 8	547	N/A = not applicable. We did not examine differences by early- vs late-onset for prior	
9	548	stillbirth/neonatal death or alcohol use due to small sample size.	
10 11	549	<sup>d</sup> IVF = in vitro fertilization	
12 13	550		
14 15 16	551		
17 18 19 20	552		
20 21 22 23	553		
24 25 26 27	554		
28 29 30	555	Figure legend	
31 32 33 34	556		
35 36 37	557	Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category	
38 39 40 41	558	(Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were	
42 43 44	559	combined. Splines with 95% confidence intervals were fitted by the generalized additive	
45 46 47 48	560	model ("gam") smoothing method.	
49 50 51	561		
52 53 54 55 56	562	Supplemental Figure 1. Flowchart of study sample selection.	
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

578	Supplementary tables					
579	9 Supplemental Table 1. Definitions and sources of variables					
		Definition	Source			
	Maternal age					
	(years)	Mother's age (in years) calculated at date of delivery.	BCPDF			
		Mother has never delivered a baby of at least 500 grams				
	Nullipara	birth weight or at least 20 weeks gestation in a previous	BCPDF			
		pregnancy.				
		Pre-existing diabetes mellitus Type 1 or Type 2, insulin				
	Pre-existing	used.	BCPDF			
	diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin				
		not used;	ICD-10			
		or 'E10','E11', 'O245','O246','O247'				

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

Mother had at least one prior stillbirth or intrauterine

Mother had in-vitro fertilization to achieve the current

The incremental sequence number of babies born from

multiple\_birth\_count. Along with mother\_id, required to

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ICD-10

**BCPDR** 

**BCPDR** 

**BCPDR** 

1 2 3	Pre-pregnancy BMI	and early- and late-onset HELLP syndrome
4 5 6 7	Chronic	
8 9 10	hypertension	010,011
11 12 13 14		Mother had at least one prior live born infa
15 16 17	Prior stillbirth	within the first 28 days of life.
18 19 20 21	/neonatal death	Mother had at least one prior stillbirth or inf
22 23 24 25		death documented.
26 27 28	IVF conception	Mother had in-vitro fertilization to achieve t
29 30 31 32		pregnancy.
33 34 35		The incremental sequence number of babi
37 38 30	Multiple destation	the current pregnancy. Should be used wit
40 41 42	maniple geolation	multiple_birth_count. Along with mother_id,
43 44 45 46		link to MULTIPLE_LABOURS.
40 47 48 49	Antepartum	
50 51 52	bleeding	
55 54 55 56		
57 58 59	_	
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< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20	BC
	weeks gestation.	
Antepartum		
	Mother had any antepartum hemorrhage or bleeding in	
bleeding or		
hemorrhage ≥ 20	pregnancy ≥ 20 weeks gestation, including bleeding from	BC
	cervical polyps.	
weeks		
	Health care provider identified intrauterine growth	
Intrauterine Growth		
	restriction (IUGR) during the antenatal period. Baby may	B
Restriction <sup>a</sup>		
	or may not be appropriately grown at birth.	
Gestational	Care provider diagnosed mother with gestational	
		BC
Hypertension	hypertension during the current pregnancy.	
Gestational	Gestational diabetes, insulin dependent.	
		B
Diabetes	Gestational diabetes, non-insulin dependent.	

Page 48 of 66

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	Care provider diagnosed proteinuria (>+1g/L) during the	
Proteinuria	current pregnancy.	
	Care provider lists mother's use of alcohol as a risk	
Alcohol use		BCPDR
	factor in this pregnancy.	
	0	
	Mother used any of the following substances at any time	
	during the current pregnancy: heroin/opioids, cocaine,	
Substance use	methadone, solvents, or marijuana; OR care provider	BCPDR
	lists use of prescription, 'other', or unknown other drug	
	as a rick to the programou	
	as a fisk to the pregnancy.	
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
	Algorithm-based estimate of gestational age at delivery.	
Gestational age at	Uses last menstrual period, first ultrasound (<20 weeks),	_
		BCPDR
delivery	clinical estimate from newborn exam, and documentation	
	from maternal chart.	

	Pre-pregnancy BMI and early- and late-onset HELLP syndrome					
		Mother was diagnosed with HELLP Syndrome (H-				
	HELLP syndrome	HELLP syndrome hemolysis, EL-elevated liver enzymes, LP-low platelet				
		count)				
0	<sup>a</sup> Ultrasound diagno	sed intra-uterine growth restriction (IUGR)				
1						
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Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and

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3	hazard ratios with 95% confidence intervals	

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

	Underweight	Normal BMI	Overweight	Obese
All pregnancies				
N cases (rate per				
thousand) <sup>a</sup>	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR <sup>b</sup>	0.78 (0.57-	Ref	1.29 (1.12-	1.62 (1.39-
or due tint	1.06)	Nei	1.49)	1.90)
Early-onset HELLP (< 34				
wks)				
N cases (rate per	8 (0 4)	125 (0 5)	73 (0 0)	60 (1 3)
thousand) <sup>a</sup>	0 (0.4)	120 (0.0)	10 (0.8)	09 (1.0)
	0.66 (0.32-	<b>-</b> <i>i</i>	1.62 (1.21-	2.37 (1.77-
Crude HK⁰	1.35)	Ket	2.16)	3.18)

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome				
4 5 6 7		Late-onset HELLP (≥ 3	34			
, 8 9 10		wks)				
11 12 13 14		N cases (rate per	35 (1 6)	462 (2 0)	199 (2 4)	145 (2 8)
15 16 17 18		thousand) <sup>a</sup>		102 (2.0)	100 (2.1)	110 (2.0)
19 20 21		Crude HR <sup>b</sup>	0.81 (0.57-	Ref	1.21 (1.02-	1.42 (1.17-
22 23 24 25			1.14)	-	1.42)	1.71)
26 27 28	584	<sup>a</sup> Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34				
29 30 31 32	585	weeks gestation (late-onset HELLP).				
33 34 35	586	<sup>b</sup> HR = hazard ratio, wit	h 95% confidence	e interval in pa	rentheses, unles	s otherwise
36 37 38 39	587	specified				
40 41 42 43	588					
44 45 46						
47 48 49 50						
51 52 53						
54 55 56 57						
58 59 60		For peer re	view only - http://bmj	open.bmj.com/site	e/about/guidelines.xl	ntml

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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

## late-onset HELLP syndrome; British Columbia, 2008/09-2019/20<sup>a</sup>

	Early-onset	Late-onset
	HELLP	HELLP
	n =275	n = 841
Pre-pregnancy BMI category	0	
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)

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome			
4 5 6 7		Nullipara	188 (68.4)	629 (74.8)	
8 9 10 11		Chronic diabetes	6 (2.2)	14 (1.7)	
12 13 14		Chronic hypertension	19 (6.9)	20 (2.4)	
15 16 17 18		Prior stillbirth /neonatal death <sup>b</sup>	<5 (<1.8)	<5 (<0.5)	
19 20 21		IVF conception <sup>c</sup>	19 (6.9)	73 (8.7)	
22 23 24 25		Multiple gestation	33 (12.0)	91 (10.8)	
26 27 28		Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)	
29 30 31 32		Antepartum bleeding/hemorrhage	15 (5 5)	12 (1 4)	
33 34 35		(≥ 20 weeks)			
36 37 38 39		Alcohol use <sup>b</sup>	<5 (<1.8)	10 (1.2)	
40 41 42		Substance use	14 (5.1)	25 (3.0)	
43 44 45 46		Smoking	14 (5.1)	36 (4.3)	
47 48 49	591	<sup>a</sup> Data shown as n(%)			
50 51 52 53	592	<sup>b</sup> Information on cell numbers <5 wa	as suppressed due	to confidentiality reasons.	
54 55 56 57	593	cIVF = in vitro fertilization			
50 59 60		For peer review only - http	o://bmjopen.bmj.com/si	te/about/guidelines.xhtml	

Page 54 of 66





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# 598 Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per

## 599 **1000 ongoing pregnancies)**<sup>a</sup>

Gestational age	Underweight	Normal BMI	Overweight	Obese
(weeks)	n = 22,392	n = 231,517	n = 83,864	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)	0.201111(0.00)	(<0.06)	0,01020 (0.00)
	<5/22332	14/220058 (0.06)	8/83600 (0 10)	6/52026 (0.11)
26-27	(<0.22)	14/230938 (0.00)	0/03009 (0.10)	0/33920 (0.11)
28-29	<5/22289 (0.04	4) 16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13	3) 22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)

Page 56 of 66

**BMJ** Open

Pre-pregnancy BM	ll and early- and la	te-onset HELLP s	yndrome 55
32-33	<5/22133 (0.14)	) 66/229249 (0.29)	29/82870 (0.35) 27/53303 (0.51)
	10/21902 (0.46)	116/227212	58/81998 (0 71) 42/52652 (0 80)
34-35	10/21002 (0.40)	(0.51)	00/01000 (0.71) 42/02002 (0.00)
	$\mathbf{\hat{\mathbf{A}}}$	154/221075	
36-37	13/21247 (0.61)	) (0.70)	70/79515 (0.88) 55/50825 (1.08)
		131/189757	
38-39	11/17845 (0.62)	(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)
<sup>a</sup> Information on ce	ll numbers <5 was	suppressed due te	o confidentiality reasons.

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome					
4 5 6 7	602	Supplemental Table 5. Demographic and clinical characteristics of women missing pre-					
8 9 10	603	pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20 <sup>a</sup>					
12 13 14		BMI not missing BMI missing					
15 16 17			n = 391,941	n = 132,536			
19 20 21		Maternal age (years)					
22 23 24		< 25	47030 (12.0)	20134 (15.2)			
25 26 27 28		25-34	247268 (63.1)	78660 (59.4)			
29 30 31		≥ 35	97643 (24.9)	33742 (25.5)			
32 33 34 35		Nullipara	189513 (48.4)	53789 (40.6)			
36 37 38		Pre-existing diabetes	2397 (0.6)	913 (0.7)			
39 40 41 42		Chronic hypertension	2847 (0.7)	890 (0.7)			
43 44 45		Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)			
40 47 48 49		IVF conception <sup>b</sup>	11549 (3.0)	3877 (2.9)			
50 51 52 53 54 55 56 57		Multiple gestation					

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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	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)				

<sup>a</sup>Data shown as n(%)

	Pre-pregnancy BMI and early- and late-onset HELLP syndrome
	<sup>b</sup> IVF = in vitro fertilization
	<sup>c</sup> Ultrasound diagnosed intra-uterine growth restriction (IUGR)
604	
605	

	Pre-pregnancy BMI and e	arly- and late-ons	set HELLP synd	rome	
606	Supplemental Table 6. Ha	zard Ratios and	95% confidence	intervals using i	imputed data
607	for missing values of BMI				
		Underweight	Normal BMI	Overweight	Obese
	Early-onset HELLP (< 34				
	wks)				
	N cases (rate per				
	thousand) <sup>a</sup>	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
		0.76 (0.43-		1.54 (1.19-	
	Adjusted HR <sup>b</sup>	1.33)	Ref	2.00)	2.06 (1.53-
	Late-onset HELLP (≥ 34				
	wks)				
	N cases (rate per		F70 (4 0)		440 (2.0)
	thousand) <sup>a</sup>	35 (1.6)	572 (1.9)	370 (2.0)	148 (2.8)
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	Underweight	Normal BMI	Overweight	Obese
arly-onset HELLP (< 34				
ks)				
N cases (rate per	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
ousand) <sup>a</sup>		( ),		~ /
	0.76 (0.43-	Ref	1.54 (1.19-	2.06 (1.53-2.78)
Adjusted HR <sup>ь</sup>	1.33)	°C2	2.00)	,
ate-onset HELLP (≥ 34				
<s)< td=""><td></td><td></td><td></td><td></td></s)<>				
N cases (rate per				
ousand) <sup>a</sup>	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)

1 2		Pre-pregnancy BMI a	nd early- and late-onset HELL	P syndrome	00
3 4 5				4.04 (0.00	
6 7			0.96 (0.51-1.8) Ref	1.24 (0.92-	1 46 (1 03-2 08)
8 9 10		Adjusted HR <sup>b</sup>		1.66)	1.10 (1.00 2.00)
11 12 13		<sup>a</sup> Rates are per 1000 c	ongoing pregnancies at 20 we	eks (early-onset HELLP	syndrome) and at
14 15 16 17		34 weeks gestation (la	ate-onset HELLP syndrome).		
18 19 20 21		<sup>⊳</sup> HR = hazard ratio, w	ith 95% confidence interval in	parentheses, unless otl	nerwise specified.
22 23 24		Adjusted for nulliparity	y, maternal age, chronic diabe	etes, chronic hypertensio	on, in vitro
25 26 27 28		fertilization, antepartu	m bleeding/hemorrhage, gest	ational diabetes, alcoho	l, substance use,
29 30 31		smoking during pregn	ancy, prior pregnancy outcom	nes, and multiple gestati	on.
32 33 34 35	608 609				
36 37 38					
39 40 41					
42 43 44 45					
46 47 48					
49 50 51					
52 53 54					
55 56 57 58					
59 60		For peer i	review only - http://bmjopen.bmj.com	/site/about/guidelines.xhtml	





Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and logtransformed 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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		BMJ Open	bmjopen-	Pag
STROBE Statemer	nt—ch	ecklist of items that should be included in reports of observational studies	2023-07913	
	Item No.	Recommendation	es es Page ≥ No.	Relevant text from manuscript
Title and abstract	1	<ul> <li>(a) Indicate the study's design with a commonly used term in the title or the abstract</li> <li>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</li> </ul>	a Title Title Page Title Page 2-3 nttp 2-3 nttp	"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."
Introduction		Iound	)://bn	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-58	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5 g	Lines 85-90
Methods			<u>j</u> .cc	
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 April	Lines 92-122
Participants	6	<ul> <li>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</li> <li>Case-control study—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</li> <li>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</li> </ul>	28, 2024 by guest. Pro	Lines 92-122
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	ected by copyrig	N/A

Page	65	of	66
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Page 65	of 66	6 BMJ Open		/bmjopen-:	
1 2 3	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7791	Lines 92-147
4 5 6 7	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 on 23 Mi	Supplemental Table 1. Definitions and sources of variables
8	Bias	9	Describe any efforts to address potential sources of bias	6-7 S	Lines 123 - 147
9 10	Study size	10	Explain how the study size was arrived at	6-722	Lines 92-147
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	Continued on next page			. Downloaded from http://bmjopen.bmj.com/ on April 28, 2024 by guest. Protected by copyright.	
43 44			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xh	tml	

		BMJ Open	bmjopen-202		Pag
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-70791	Lines 123 - 147	
Statistical	12	( <i>a</i> ) Describe all statistical methods, including those used to control for confounding	6-7 o	Lines 123 – 147	
methods		(b) Describe any methods used to examine subgroups and interactions	n 6-7 ະນ	Lines 123 – 147	
		(c) Explain how missing data were addressed	6-7≦	Lines 123 - 147	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	N/AS		
		Case-control study-If applicable, explain how matching of cases and controls was addressed	202		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	4. Dow		
		( <u>e</u> ) Describe any sensitivity analyses	6-7 a	Lines 123 - 147	
Results		6	ded		
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially eligible, examined	7-8 from	Lines 149-164	
		for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	http		
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164	
		(c) Consider use of a flow diagram	29 号.	Supplemental Figure 1	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164	
		(b) Indicate number of participants with missing data for each variable of interest	7-88	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*	Cohort study—Report numbers of outcome events or summary measures over time	7-8≥	Lines 149-164	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	nil N		
		Cross-sectional study—Report numbers of outcome events or summary measures	28, 2		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	8-92	Lines 165-212	
		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were	t by		
		included	gue		
		(b) Report category boundaries when continuous variables were categorized	5 st. F	Lines 105-106	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/AQ		
		period	ecte		
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#### BMJ Open

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Other analyses Discussion Key results Limitations Interpretation	17 18 19	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Summarise key results with reference to study objectives	3-079131 11 c	Lines 213-216
Discussion Key results Limitations Interpretation	18 19	Summarise key results with reference to study objectives	11 c	
Key results Limitations Interpretation	18 19	Summarise key results with reference to study objectives	11 0	T:
Limitations Interpretation	19		· · · ~	Lines 220-229
Interpretation		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13- <b>යි</b> කූ	Lines 280-307
	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-EP 202	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-5	Lines 280-307
Other informatio	n		own	
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	Titløpa;	ge
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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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<b>Primary Subject Heading</b> :	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Obesity, EPIDEMIOLOGY, OBSTETRICS





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2 3 4 5	1	Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset
6 7 8	2	hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-
9 10 11 12	3	based retrospective cohort study.
13 14 15	4	Authors
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58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	17	6. School of Population and Public Health, University of British Columbia,
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22 23 24	22	Work: 604-875-3015; Cell: 778-513-1648; Email: liqing.wang@bcchr.ca
25 26 27	23	
28 29 30	24	Abstract
30 31 32 33	25	Background: Obesity increases risk of pre-eclampsia, but the association with
34 35 36	26	hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
37 38 39 40	27	understudied.
41 42 43	28	Objective: To examine the association between pre-pregnancy body-mass-index (BMI)
44 45 46 47	29	and HELLP syndrome, including early- vs. late-onset disease.
48 49 50	30	Study Design: A retrospective cohort study using population-based data.
51 52 53 54	31	Setting: British Columbia (BC), Canada, 2008/09-2019/20.
55 56 57	32	<b>Population:</b> All pregnancies resulting in live births or stillbirths at $\geq$ 20 weeks' gestation.
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	3
4 5 6	33	Methods: BMI categories (kg/m <sup>2</sup> ) included: underweight (<18.5), normal (18.5-24.9),	
7 8 9 10	34	overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP	
11 12 13	35	syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing	
14 15 16 17	36	pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to	
18 19 20 21	37	assess the associations between risk factors (e.g., BMI, maternal age and parity) and	
22 23 24	38	early- vs late-onset HELLP syndrome.	
25 26 27 28	39	Main outcome measures: Early- and late-onset HELLP syndrome.	
29 30 31	40	Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases	)
32 33 34 35	41	among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI,	
36 37 38	42	overweight and obese categories, respectively. Overall, gestational age-specific rates of	of
39 40 41 42	43	HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal	
43 44 45	44	BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard	t
46 47 48 49	45	ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP	
50 51 52 53 54	46	syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic	
55 56 57 58			

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	47	hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also
8 9 10	48	showed differing AHRs between early- vs. late-onset HELLP syndrome.
12 13 14	49	Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the
15 16 17	50	association is stronger with early-onset HELLP syndrome. Associations with early- and
18 19 20 21	51	late-onset HELLP syndrome differed for some risk factors, suggesting possible
22 23 24	52	differences in etiologic mechanisms.
25 26 27 28	53	Strengths and limitations of this study
29 30 31	54	We were able to describe gestational age-specific incidence of HELLP
32 33 34	55	syndrome, based on population data on all pregnancies.
35 36 37 38	56	The population-based design coupled with detailed information about
39 40 41	57	demographic, behavioural and clinical factors allowed robust adjustment for
42 43 44 45	58	possible confounding.
46 47 48	59	• We did not have detailed information on laboratory values used for the diagnosis
49 50 51 52	60	of HELLP syndrome and therefore we were not able to estimate the severity of
53 54 55 56	61	HELLP syndrome.
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Pre-pregnancy BMI and early- and late-onset HELLP syndrome We did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome. Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had missing information about BMI. We used multiple imputation methods to address this limitation. Key words Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity, pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP syndrome. Word count: 3036 Introduction Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies 

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	77	worldwide(1,2) and accounting for up to 14% of maternal deaths.(3) Early-onset PE at
7 8 9 10	78	<34 weeks' gestation is often associated with placental insufficiency whereas late-onset
11 12 13 14	79	PE is often associated with pre-existing maternal health conditions such as metabolic
15 16 17	80	syndrome and obesity.(4) Early- vs late-onset PE differ with regard to some risk factors,
18 19 20 21	81	clinical management and rates of adverse perinatal outcomes.(5,6) A related condition,
22 23 24	82	namely, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs
25 26 27 28	83	in 0.2-0.8% of pregnancies(7–9) and 10-20% of cases of severe PE.(10) Although
20 29 30 31	84	HELLP syndrome has been distinguished from PE as a separate disease,(11) it is still
32 33 34 35	85	commonly viewed as a form of severe PE.(9) While the distinction between early- and
36 37 38	86	late-onset PE and the difference in the associations between pre-pregnancy obesity and
39 40 41 42	87	these conditions has been established, such differences have not been studied with
43 44 45	88	regard to HELLP syndrome.
46 47 48	89	Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–
49 50 51 52	90	15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the
53 54 55 56	91	proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The
57 58 59		
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Pre-pregnancy BMI and early- and late-onset HELLP syndrome prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18) and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in high income countries, the association between maternal pre-pregnancy body-mass-index (BMI) and HELLP syndrome has not been adequately assessed in a large population-based study to date. We carried out a population-based, retrospective cohort study to examine the association between maternal pre-pregnancy BMI and HELLP syndrome and to assess differences in this association in early- vs late-onset HELLP syndrome. We hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this relationship may be different in early- compared with late-onset disease. In additional analyses, we examined other risk factors for HELLP syndrome in terms of their association with early- vs late-onset HELLP syndrome. Materials and Methods Data sources and study population 

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	106	The study included all live births and stillbirths at ≥20 weeks' gestation in British
, 8 9 10	107	Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from
11 12 13 14	108	the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes
15 16 17	109	information on >99% of births in BC, with detailed data on maternal demographic
18 19 20 21	110	characteristics, prenatal care, pregnancy complications, labor and delivery
22 23 24	111	characteristics and neonatal outcomes. Each record, abstracted from medical charts (or
25 26 27 28	112	midwives' notes), includes up to 25 International Classification of Diseases, 10 <sup>th</sup> Edition,
28 29 30 31	113	Canadian version (ICD-10-CA) codes for diagnoses related to the delivery
32 33 34	114	hospitalization. Chart abstraction is standardized and conducted by trained personnel,
35 36 37 38	115	and data quality is routinely assessed. Prior validation studies showed high accuracy of
39 40 41 42 43	116	collected information on labor and delivery.(21)
44 45 46	117	Pre-pregnancy BMI and HELLP syndrome
47 48 49 50	118	Pre-pregnancy weight and height were based on maternal self-report or health care
51 52 53	119	provider assessment at $\leq$ 11 weeks' gestation.(22) BMI was classified as follows (in
54 55 56 57 58	120	kg/m <sup>2</sup> ): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

			9
1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
4 5 6 7	121	(≥30.0).(23) The primary outcome of this study was a physician diagnosis of HELLP	
8 9 10	122	syndrome documented in the medical chart, and abstracted and recorded in the	
11 12 13 14	123	BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee	
15 16 17	124	classification criteria, namely lactate dehydrogenase≥600 IU/I, liver transaminases	
18 19 20	125	(aspartate aminotransferase and alanine aminotransferase) elevated more than twice the	
21 22 23	126	upper limit of normal, and a platelet count <100,000/ $\mu$ l (109/l).(24) Early- and late-onset	
24 25 26 27	127	HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks and	
28 29 30	128	≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to ascertain	
31 32 33	129	gestational age, and the last menstrual period estimate of gestational age was used for	r
34 35 36 37	130	those without early pregnancy ultrasound information.	
38 39 40 41	131	Covariates	
42 43 44	132	In addition to BMI, we examined the association between maternal age, nulliparity, pre-	-
45 46 47	133	existing diabetes, chronic hypertension, <i>in vitro</i> fertilization (IVF) conception, multiple	
49 50 51	134	gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance	
52 53 54 55 56 57 58 59	135	use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcoho	I

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	Pre-pregnancy BMI and early- and late-onset HELLP syndrome
136	use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as
137	potential confounders; all these factors are known to be associated with HELLP
138	syndrome.(25) Maternal age was categorized as <25, 25-34 and $\geq$ 35 years. All chronic
139	conditions and pregnancy complications were identified using ICD-10 codes or data
140	fields abstracted from medical charts to the BCPDR (Table A.1).
141	Statistical analyses
142	The rates of HELLP syndrome per 1000 deliveries were compared between women in
143	each BMI category. Complete case analyses were performed for individuals with known
144	BMI. The association between pre-pregnancy BMI and HELLP syndrome was first
145	expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained
146	from a Cox model without adjustment for other risk factors.
147	Gestational age-specific rates of HELLP syndrome were compared between
148	women in the various BMI categories, using undelivered pregnancies at each
149	gestational week as the denominator. These rates were plotted, and splines with 95%
150	confidence intervals were fitted by the generalized additive model ("gam") smoothing
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	<ol> <li>136</li> <li>137</li> <li>138</li> <li>139</li> <li>140</li> <li>141</li> <li>142</li> <li>143</li> <li>144</li> <li>145</li> <li>146</li> <li>147</li> <li>148</li> <li>149</li> <li>150</li> </ol>

1		11
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	151	method. Cox models with interaction terms between pre-pregnancy BMI categories and
8 9 10	152	gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain
11 12 13 14	153	crude HRs and 95% Cis. This analysis was carried out to assess whether gestational
15 16 17	154	age at onset modified the association between BMI and HELLP syndrome.
18 19 20 21	155	In multivariable analyses, Cox models were also used to adjust for covariates
22 23 24	156	(listed above) and to also examine their associations with early- vs late-onset of HELLP
25 26 27 28	157	syndrome using interaction terms. We did not assess early- vs late-onset of HELLP
29 30 31	158	syndrome interactions with risk factors including alcohol use and prior adverse birth
32 33 34 35	159	outcomes due to a low number of women with HELLP syndrome in these categories,
36 37 38	160	but adjusted for them in the model as potential confounders.
39 40 41 42	161	Sensitivity analyses included multiple imputations for missing BMI values based
42 43 44 45	162	on a multiple imputation procedure using SAS statistical software (PROC MI).(26)
46 47 48	163	Variables included in the imputation were those also included in the regression
49 50 51 52 53 54 55 56 57	164	analyses. Ten imputed datasets were created, with the final results obtained using
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	165	Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were
, 8 9 10	166	compared with the primary analyses.
11 12 13 14	167	All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
15 16 17	168	NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British
18 19 20 21	169	Columbia/Children's and Women's Hospital and Health Centre of British Columbia
22 23 24	170	Research Ethics Board (#H20-03985).
25 26 27 28	171	Patient and Public Involvement
29 30 31	172	Neither patients nor the public were involved in the design, or conduct, or reporting, or
32 33 34 35	173	dissemination plans of our research.
36 37 38 39	174	
40 41 42	175	Results
43 44 45 46	176	Study population
47 48 49	177	Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,
50 51 52 53	178	2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational
54 55 56	179	age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	180	study population for the primary analyses included 391,941 pregnancies, after exclusion
8 9 10	181	of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP
11 12 13 14	182	syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).
15 16 17	183	The proportion of women who were in underweight, normal BMI, overweight and
18 19 20 21	184	obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively.
22 23 24	185	Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes
25 26 27 28	186	(stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational
29 30 31	187	diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women
32 33 34 35	188	with overweight and obesity compared with women with normal BMI (Table 1).
36 37 38	189	Nulliparity and ultrasound diagnosed fetal growth restriction were observed more
39 40 41 42	190	frequently in the underweight group. Substance use and smoking during pregnancy
43 44 45	191	were more frequent in underweight, overweight, and obese groups compared with
46 47 48 49	192	women with normal BMI.
50 51 52	193	
53 54 55 56 57 58	194	Unadjusted analyses for pre-pregnancy BMI
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 4 5 6	195	The rates of HELLP syndrome in women in underweight, normal, overweight, and
7 8 9	196	obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table
10 11 12 13	197	2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and
14 15 16 17	198	obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),
18 19 20	199	respectively, compared with women who had normal BMI (Table A.2).
21 22 23 24	200	The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2
25 26 27	201	(n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,
28 29 30 31	202	respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks
32 33 34	203	(75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older
35 36 37 38	204	maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation,
39 40 41 42	205	bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance
42 43 44 45	206	use and smoking were higher among women with early-onset vs. late-onset HELLP
46 47 48 49	207	syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity,
50 51 52	208	IVF conception, and alcohol use were higher among women with late-onset HELLP
53 54 55 56	209	syndrome (Table A.3).
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1			15
2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	210	The rates of late-onset HELLP syndrome were higher than early-onset HELLP	
8 9 10 11	211	syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous	
12 13 14	212	women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal	
15 16 17 18	213	death, IVF conception, multiple gestation, alcohol use and substance use also had	
19 20 21	214	higher rates of late-onset than early-onset HELLP syndrome. Women with multiple	
22 23 24 25	215	gestation had highest rate of HELLP syndrome, followed by those with chronic	
26 27 28	216	hypertension.	
29 30 31	217	Differences in gestational age-specific incidence rates of HELLP syndrome by	
33 34 35	218	BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational	-
36 37 38 20	219	age specific rates).	
40 41 42	220	Gestational age-specific rates of HELLP syndrome increased over the course of	
43 44 45	221	pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women	
46 47 48 49	222	with pre-pregnancy BMI below or above normal values but not among those with norm	al
50 51 52	223	BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP	
53 54 55 56 57 58 59	224	syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) an	d

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	225	2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These
8 9 10	226	HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP
11 12 13 14	227	syndrome, respectively (Table A.2).
15 16 17	228	
18 19 20 21	229	Adjusted analyses
22 23 24	230	The associations did not change substantially after adjusting for other risk factors (Table
25 26 27 28	231	3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on
29 30 31	232	HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly
32 33 34	233	associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP
36 37 38	234	syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).
39 40 41 42	235	Adjusted hazard ratios (AHR) for each risk factor calculated separately for early-
43 44 45	236	vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly
46 47 48	237	associated with HELLP syndrome included overweight, obesity, advanced maternal age
50 51 52	238	(≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation,
53 54 55 56	239	and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse
57 58 59		
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xntmi

1 2 3		17 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	240	association with HELLP syndrome. IVF conception was a risk factor for late-onset but
8 9 10	241	not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
11 12 13 14	242	bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
15 16 17	243	syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation
18 19 20 21	244	(p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage
22 23 24	245	(p=0.011) differed significantly in their associations with early versus late-onset HELLP
25 26 27 28	246	syndrome (p-values for interaction).
29 30 31	247	Sensitivity analyses
32 33 34 35	248	Women with missing BMI were not substantially different from women with known BMI
36 37 38	249	(Table A.5); and the results were not appreciably changed after the analyses were
39 40 41 42	250	repeated using imputed BMI values (Table A.6).
43 44 45	251	
46 47 48 49	252	Discussion
50 51 52 53 54 55 56 57 58 59	253	Main findings

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6	254	To our knowledge, this is the largest contemporary study examining the association
7 8 9 10	255	between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
11 12 13	256	disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
15 16 17	257	34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
18 19 20 21	258	lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
22 23 24	259	were at elevated risk for developing HELLP syndrome. Obesity was more strongly
25 26 27 28	260	associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
29 30 31	261	study showed that chronic hypertension, bleeding before 20 weeks' gestation and
32 33 34 35	262	antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP
36 37 38	263	syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP
39 40 41 42	264	syndrome.
43 44 45	265	Interpretation in the context of scientific literature
46 47 48 49	266	The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the
50 51 52	267	previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-
53 54 55 56 57	268	2016.(25) Prior studies describing the association between pre-pregnancy obesity and
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	269	HELLP syndrome are sparse and results vary. In a retrospective cohort study from a
8 9 10	270	single tertiary hospital in the United States (n=434), Martin <i>et al.</i> found that maternal
11 12 13 14	271	weight was not associated with HELLP syndrome.(29) Similarly, a case-control study
15 16 17	272	(n= 129 cases and 476 controls) found no association between obesity and HELLP
18 19 20 21	273	syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases
22 23 24	274	and 601 controls) showed that pre-pregnancy BMI was associated with PE but not
25 26 27 28	275	HELLP syndrome and suggested that PE and HELLP may have different
29 30 31	276	pathophysiology.(12) In contrast, a population-based cohort study from Norway
32 33 34 35	277	(n=418,897) found that pre-pregnancy BMI ≥30kg/m² was associated with HELLP
36 37 38	278	syndrome in the first but not the second pregnancy.(9) However, in that study, only 25%
39 40 41 42	279	of women with a first pregnancy and 30% of women with their second pregnancy had
43 44 45	280	information on BMI. More recently, a population-based study from Canada
46 47 48 49	281	(n=1,078,323) showed that obesity documented in medical charts was a risk factor for
50 51 52	282	HELLP syndrome,(31) however, obesity rates were underestimated and information on
53 54 55 56 57	283	BMI was not available, precluding more detailed analyses.
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	284	While PE is typically recognized as early- vs late-onset disease (before vs $\geq$ 34
7 8 9 10	285	weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A
11 12 13 14	286	prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is
15 16 17	287	a stronger risk factor for late-onset PE than early-onset PE.(15) That study also
18 19 20 21	288	demonstrated a correlation between increased prevalence of maternal obesity in
22 23 24	289	parallel with late-onset PE during the 18-year period, while the incidence of early-onset
25 26 27 28	290	PE stayed relatively constant.(15) In contrast, our study shows a stronger association
29 30 31	291	between overweight/obesity and early-onset HELLP syndrome compared with late-
32 33 34 35	292	onset HELLP syndrome. This suggests varying pathophysiological pathways between
36 37 38	293	PE and HELLP syndrome or additional obesity-related pathophysiology associated with
39 40 41 42	294	PE that leads to liver damage at earlier gestation, for instance, obesity-associated
43 44 45	295	steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age
46 47 48	296	cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
49 50 51 52	297	However, our data suggest an increase in gestational age-specific rates after 28 weeks'
53 54 55 56 57	298	gestation in women with obesity and after 30 weeks' gestation in women without
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1		2:
2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	299	obesity. A previous study showed a high proportion of HELLP syndrome cases
8 9 10	300	occurring between 27 and 37 weeks, (33) which indicates potential dissimilarities with
11 12 13 14	301	early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk
15 16 17	302	factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-
18 19 20 21	303	onset disease. It is worth mentioning that the known inverse association between
22 23 24	304	smoking and PE(6) was also observed in HELLP syndrome in our study, and this
25 26 27 28	305	warrants further investigation.
29 30 31	306	Clinical and research implications
32 33 34 35	307	Our findings show that increases in gestational age-specific rates of HELLP syndrome
36 37 38	308	vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in
39 40 41 42	309	women who were in the underweight, overweight and obese categories, but continued
43 44 45	310	increasing in women with normal BMI. This could be due to higher rates of medically
46 47 48	311	indicated early-term deliveries in groups with low or high BMI, which has been shown to
49 50 51 52	312	reduce maternal morbidity compared with expectant management.(34) It is possible that
53 54 55 56 57 58 59	313	women whose pre-pregnancy BMI was below and above normal range were more likely

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	314	to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and
8 9 10	315	therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal
11 12 13 14	316	and infant outcomes. However, further research in needed to confirm this hypothesis. In
15 16 17	317	addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks'
18 19 20 21	318	gestation and antepartum bleeding/hemorrhage were more strongly associated with
22 23 24	319	early- onset HELLP syndrome, while multiple gestation was more strongly associated
25 26 27 28	320	with late-onset HELLP syndrome. The association between bleeding at <20 weeks gestation
29 30 31	321	and early-onset HELLP syndrome is novel. Such bleeding can be caused by abnormal
32 33 34	322	placental conditions (e.g., abnormal implantation and associated bleeding), which may
36 37 38	323	play a role in the development of HELLP syndrome. These findings are exploratory and
39 40 41 42	324	require confirmation by other studies. However, they raise the intriguing possibility that
43 44 45	325	determinants of HELLP syndrome (such as antepartum bleeding) have different
46 47 48 49	326	associations with early and late onset HELLP syndrome depending on whether they
50 51 52	327	occur at <20 weeks or at $\ge$ 20 weeks' gestation. In our study, the association between
53 54 55 56 57	328	antepartum bleeding at $\geqslant$ 20 weeks' gestation and HELLP syndrome (which could
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1		2	3
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	329	have been explained as being a consequence of HELLP syndrome causing placental	
8 9 10	330	abruption) was not significant in adjusted models.	
11 12 13 14	331	Strengths and limitations	
15 16 17	332	The strengths of this study include its population-based design coupled with detailed	
18 19 20 21	333	information about demographic, behavioural and clinical factors that allowed for robust	
22 23 24	334	adjustment for possible confounding. We had a large enough sample to provide precise	;
25 26 27 28	335	estimates for associations with HELLP syndrome, a rare outcome.	
29 30 31	336	This study also has several limitations. First, we did not have detailed information	า
32 33 34 35	337	on laboratory values important for the diagnosis of HELLP syndrome and therefore we	
36 37 38	338	were not able to estimate the severity of HELLP. We assumed that the diagnosis of	
39 40 41 42	339	HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal	
43 44 45	340	condition. However, in milder cases, expectant management with close observation	
46 47 48 40	341	may have led to a delay between the diagnosis and delivery, especially at very preterm	
49 50 51 52	342	gestation. As a result, incidence of early-onset HELLP syndrome may have been	
53 54 55 56 57 58	343	underestimated in our study. However, we do not expect a large inaccuracy in this	

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	344	regard because HELLP syndrome is considered a potentially life-threatening condition
8 9 10	345	and delivery is typically not delayed. Second, we did not have information about
12 13 14	346	race/ethnicity, socio-economic status (SES) and prior history of pregnancy with
15 16 17	347	PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding
19 20 21	348	in the assessments of the relation between BMI and HELLP syndrome. However, we
22 23 24	349	adjusted for several possible confounders and did not observe changes in the
25 26 27 28	350	association between BMI and HELLP syndrome, suggesting that our results are robust.
29 30 31	351	Third, pre-pregnancy BMI was largely self-reported, which may have led to some
32 33 34 35	352	misclassification. Several validation studies have shown relatively good accuracy of
36 37 38	353	self-reported weight and height for epidemiological studies,(35–37) suggesting that a
39 40 41 42	354	large misclassification bias is unlikely. A systematic review of BMI self-report
43 44 45	355	misclassification showed minimal influence on associations between BMI and
46 47 48 49	356	pregnancy outcomes.(38)
50 51 52	357	Approximately 25% of women had missing information about BMI. These women
53 54 55 56 57	358	were relatively similar to those with known BMI and sensitivity analyses using imputed
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Pre-pregnancy BMI and early- and late-onset HELLP syndrome BMI values yielded results almost identical to the main analyses. Lastly, the analyses examining differences between early- and late-onset HELLP and risk factors other than BMI were exploratory, and further studies are required to confirm our findings. Conclusions Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk factor for HELLP syndrome. However, contrary to the documented association between BMI and PE, with obesity being associated more strongly with late-onset than early-onset PE, our study showed that obesity was more strongly associated with early-onset than with late-onset HELLP syndrome. This suggests potentially different underlying pathophysiology for the various hypertensive disorders of pregnancy. Our findings can help maternity care providers with regard to pre-pregnancy counselling. Clinicians can better identify women who may benefit from obstetric intervention, as the risk of HELLP increases at late pre-term gestation in all women and continues to increase at term and post-term gestation in women with normal pre-pregnancy BMI. More research on the 

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	374	gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the
, 8 9 10	375	underlying causes of HELLP syndrome.
11 12 13	376	
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34		
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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	
5 6 7	377	Disclosure	
8 9 10 11	378	The authors report no conflict of interest.	
12 13 14 15	379	Disclaimer	
16 17 18	380	All inferences, opinions, and conclusions drawn in this publication are those of the	
19 20 21 22 23	381	authors, and do not reflect the opinions or policies of Perinatal Services BC.	
24 25 26 27	382	Author Statement/Contribution to Authorship	
28 29 30	383	LW and SL were involved in the conception, planning, carrying out and analyzing data	a
31 32 33 34	384	of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.	
35 36 37	385	LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KS.	J,
38 39 40 41	386	NR.	
43 44 45	387	Acknowledgement	
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49 50 51 52	389	to the BCPDR database.	
53 54 55 56 57 58 59	390	Funding statement	

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	391	This study was funded by the Canadian Institutes for Health Research (CIHR) and the
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15 16 17	394	Research Institute, Canada, NR is supported by a grant from the Swedish Research
18 19 20 21	395	Council for Health, Working Life and Welfare (grant no. 2019-00041). The funding
22 23 24	396	sources were not involved in study design, data collection, analysis, and interpretation,
25 26 27 28	397	writing of the manuscript, and/or decision to submit the article for publication.
29 30 31	398	
32 33 34 35	399	Competing interests statement
36 37 38	400	The authors report no conflict of interest.
39 40 41 42	401	Data availability
43 44 45	402	Data may be obtained from a third party and are not publicly available.
46 47 48 49	403	Ethics Approval Statement
50 51 52 53		
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1 2 3		Pre	e-pregnancy BMI and early- and late-onset HELLP syndrome				
4 5 6 7	404	Ethics approval was obtained from the University of British Columbia/Children's and					
8 9 10	405	Wo	omen's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-				
12 13 14	406	03	985).				
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Page 32 of 56

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6	524	
7 8 9 10	525	
11 12 13	526	
14         15         14         15         16         17         18         10         21         22         24         25         26         27         28         30         31         32         33         34         35         36         37         38         40         41         42         43         44         50         51         52         53	527	
55 56 57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Pre-pregnancy	BMI and	early- and	late-onset HEL	LP syndrome
		<b>j</b>		- ,

#### 528 Tables

## Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-

# 530 mass-index; British Columbia, 2008/09-2019/20<sup>a</sup>

	Underweigh	tNormal 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 <sup>b</sup>	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 <sup>d</sup>	<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 <sup>c</sup>	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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1						36		
2 3 4		Pre-pregnancy BMI and ea	rly- and late-o	onset HELLP s	yndrome			
5		Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)		
7		Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)		
8 9		Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)		
10 11		Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)		
12 13		Gestational age at delivery	,					
14 15		(weeks)						
16 17		20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)		
17 18 19 20 21 22 23		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)		
24 25		≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)		
26 27	531	<sup>a</sup> Data shown as n(%)						
28 29	532	<sup>b</sup> IVF = in vitro fertilization						
30 31	533	<sup>c</sup> Ultrasound diagnosed intra-uterine growth restriction (IUGR)						
32 33	534	<sup>d</sup> Information on cell numbers <5 was suppressed due to confidentiality reasons.						
34	535	Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing						
35 36	536	pregnancies by maternal demographic and clinical characteristics; British Columbia,						
37 38	537	7 2008/09-2019/20						
39 40				Early-onse	t Late-ons	et		
41 42				HELLP	HELLP	Overall		
43				syndrome	syndrom	e		
44 45		Pre-pregnancy BMI category						
46 47		Underweight		8 (0.4)	35 (1.6)	43 (1.9)		
48 49		Normal weight		125 (0.5)	462 (2.0)	587 (2.5)		
50 51		Overweight		73 (0.9)	199 (2.4)	272 (3.2)		
52		Obese		69 (1.3)	145 (2.8)	214 (4.0)		
54		Maternal age (years)						
55 56 57		< 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 deatha	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception <sup>b</sup>	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 <sup>a</sup>	<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)
	25-34 ≥ 35 Nullipara Pre-existing diabetes Chronic hypertension Prior stillbirth /neonatal death <sup>a</sup> IVF conception <sup>b</sup> Multiple gestation Bleeding (< 20 weeks) Antepartum Bleeding/hemorrhage (≥ 20 weeks) Alcohol use <sup>a</sup> Substance use Smoking	$25-34$ $158 (0.6)$ $\geq 35$ $87 (0.9)$ Nullipara $188 (1.0)$ Pre-existing diabetes $6 (2.5)$ Chronic hypertension $19 (6.7)$ Prior stillbirth /neonatal death <sup>a</sup> $<5 (<1.0)$ IVF conception <sup>b</sup> $19 (1.6)$ Multiple gestation $33 (5.6)$ Bleeding (< 20 weeks)	$25-34$ $158 (0.6)$ $512 (2.1)$ $\geq 35$ $87 (0.9)$ $232 (2.4)$ Nullipara $188 (1.0)$ $629 (3.4)$ Pre-existing diabetes $6 (2.5)$ $14 (6.3)$ Chronic hypertension $19 (6.7)$ $20 (7.7)$ Prior stillbirth /neonatal death <sup>a</sup> $<5 (<1.0)$ $<5 (<1.0)$ IVF conception <sup>b</sup> $19 (1.6)$ $73 (6.7)$ Multiple gestation $33 (5.6)$ $91 (19.3)$ Bleeding (< 20 weeks)

<sup>30</sup> <sub>31</sub> 538 <sup>a</sup>Information on cell numbers <5 was suppressed due to confidentiality reasons. Other

 $\frac{32}{33}$  539 numbers were suppressed if needed to avoid back-calculation from the total

540 <sup>b</sup>IVF = in vitro fertilization

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 36 541
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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
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.62
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)	0.12
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.02
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.99
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)	0.44
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.22
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.27
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.04
Prior stillbirth/neonatal death <sup>c</sup>	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception <sup>d</sup>	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.10
Multiple gestation	13.66 (11.06- 16.87)	8.31 (5.59- 12.35)	17.81 (13.89- 22.83)	0.00
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.00
Antepartum bleeding or hemorrhage ( $\geqslant$ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.01
Alcohol use <sup>c</sup>	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)	0.16
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.96

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5	546	<sup>b</sup> p-value for interaction with early- vs late-onset HELLP syndrome.
6 7	547	°N/A = not applicable. We did not examine differences by early- vs late-onset for prior
8	5/18	stillbirth/neonatal death or alcohol use due to small sample size
9	540	
10	549	"IVF = In vitro fertilization
12 13 14	550	
15 16 17	551	
18 19 20	552	
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22 23	553	
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25 26	554	
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28	555	Figure legend
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32 33	556	
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35 36	557	Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category
37		
38		
39 40	558	(Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were
41		
42 43	559	combined. Splines with 95% confidence intervals were fitted by the generalized additive
44		
45 46		
40 47	560	model ("gam") smoothing method.
48		
49 50	561	
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52 52		
55 54	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 logtransformed 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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Supplementary tables	en-2023-07	
Supplemental Table 1.	. Definitions and sources of variables	
	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDF
N. U.	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gesta	tion
Nullipara	in a previous pregnancy.	BCPDF
	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used.	BCPDI
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used;	
	or 'E10','E11', 'O245','O246','O247'	ICD-1
Chronic hypertension	'010','011'	ICD-1
Prior stillbirth	Mother had at least one prior live born infant, who died within the first 28 days of life.	
/neonatal death	Mother had at least one prior stillbirth or intrauterine death documented. $\aleph$	BCPD
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPD
	The incremental sequence number of babies born from the current pregnancy. Should be used	
Multiple gestation	with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABO RS.	BCPD
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Page 44 of 56

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Antepartum bleeding	02 3-077	
< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation. $3$	BC
Antepartum	Mare Nare	
bleeding or	Mother had any antepartum hemorrhage or bleeding in pregnancy $\geq$ 20 weeks gestation, including $\frac{3}{4}$	B B
hemorrhage ≥ 20	bleeding from cervical polyps.	D
weeks	loaded f	
Intrauterine Growth	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period.	D
Restriction <sup>a</sup>	Baby may or may not be appropriately grown at birth.	B
Gestational		
Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	B
Gestational Diabetes	Gestational diabetes, insulin dependent.	B
	Gestational diabetes, non-insulin dependent.	D
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy. ୧୯	B
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	B
	ected by	
	v copyri	
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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 $\widehat{S}$	BCPDR
	prescription, 'other', or unknown other drug as a risk to the pregnancy. 조	
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultraso	und
delivery	(<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low	
HELLP syndrome	platelet count)	BCPDR
°Ultrasound diagnos	ed intra-uterine growth restriction (IUGR)	
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Page 47 of 56	5
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	Underweight			
	5	Normal Bivii	Overweight	obese S N
l pregnancies				3 Marc
N cases (rate per thousand) <sup>a</sup>	43 (1.9)	587 (2.5)	272 (3.2)	202 214 (4.0)
Crude HR <sup>b</sup>	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
arly-onset HELLP (< 34 wks)				loaded
N cases (rate per thousand) <sup>a</sup>	8 (0.4)	125 (0.5)	73 (0.9)	from 69 (1.3)
Crude HR <sup>b</sup>	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)
ite-onset HELLP (≥ 34 wks)				open.br
N cases (rate per thousand) <sup>a</sup>	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR <sup>b</sup>	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	P P 1.42 (1.17-1.71)
ates are per 1000 ongoing pregnar	ncies at 20 weeks (early	/-onset HELLP) and a	at 34 weeks gestation (late-	oniset HELLP).
R = hazard ratio, with 95% confide	nce interval in parenth	eses, unless otherwi	se specified	24 by (
				juest.
				Pro

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upplemental Table 3. Maternal o 008/09-2019/20ª	demographic and clinica	al characteristics by early	/- vs late-onset HELLP sy	yndrome; British Columbia
	Early-onset HEL	LP Late-onset HELLP	-	n 23 Ma
	n =275	n = 841		rch 2024
re-pregnancy BMI category	0		-	Downl
Underweight	8 (2.9)	35 (4.2)		oaded f
Normal weight	125 (45.5)	462 (54.9)		rom http
Overweight	73 (26.6)	199 (23.7)		o://bmjo
Obese	69 (25.1)	145 (17.2)		pen.bm
Maternal age (years)				j.com/ c
< 25	30 (10.9)	97 (11.5)		n April
25-34	158 (57.5)	512 (60.9)		28, 202
≥ 35	87 (31.6)	232 (27.6)		4 by gue
Nullipara	188 (68.4)	629 (74.8)		st. Prot
Chronic diabetes	6 (2.2)	14 (1.7)		ected b
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	i or peer review only - III	ap.//binjopen.binj.com/site	, about, guidennes.xntml	

e 49 of 56			BMJ Open
	Chronic hypertension	19 (6.9)	20 (2.4)
	Prior stillbirth /neonatal death <sup>b</sup>	<5 (<1.8)	<5 (<0.5)
	IVF conception <sup>c</sup>	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 <sup>b</sup>	<5 (<1.8)	10 (1.2)
	Substance use	14 (5.1)	25 (3.0)
	Smoking	14 (5.1)	36 (4.3)
	<sup>a</sup> Data shown as n(%)		`C
	<sup>b</sup> Information on cell numbers <5 was s	uppressed due to co	nfidentiality reasons.
	<sup>CIVE</sup> - in vitro fortilization		

 VF = IN VITO fertilization

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Gestational age	Underweight	Normal BMI	Overweight	– <del>3</del> Obese
(weeks)	n = 22,392	n = 231,517	n = 83,864	5 23 Man = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	2x5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	0 45/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	ຊີ 65/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	ğ 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)	9 <u>4</u> 2/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	ಜ್ ಜ್ಞ5/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	بة 5 236/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	ន្ត្ ជា2/15135 (0.79)

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	BMI not missing	BMI missing	_
	n = 391,941	n = 132,536	
Naternal age (years)	0		_
< 25	47030 (12.0)	20134 (15.2)	
25-34	247268 (63.1)	78660 (59.4)	
≥ 35	97643 (24.9)	33742 (25.5)	
lullipara	189513 (48.4)	53789 (40.6)	
Pre-existing diabetes	2397 (0.6)	913 (0.7)	
Chronic hypertension	2847 (0.7)	890 (0.7)	
rior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)	
VF conception <sup>b</sup>	11549 (3.0)	3877 (2.9)	
Aultiple gestation			
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 <sup>c</sup>	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)

<sup>a</sup>Data shown as n(%)

<sup>b</sup>IVF = in vitro fertilization

<sup>c</sup>Ultrasound diagnosed intra-uterine growth restriction (IUGR)

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**BMIOnen** 

Page 53	of 56
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		BMJ Open		I 136/bmj
Supplemental Table 6. Hazar	<sup>r</sup> d Ratios and 95% confidence inter	rvals using imputed data	a for missing values of BI	open-2023 <b>要</b> 7%
	Underweight	Normal BMI	Overweight	<u>9</u> 1 Obese
Early-onset HELLP (< 34 wks	;)			23 Mar
N cases (rate per thousand	d) <sup>a</sup> 8 (0.4)	164 (0.5)	137 (0.9)	유 2071 (1.3)
Adjusted HR <sup>b</sup>	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2
Late-onset HELLP (≥ 34 wks)				loaded
N cases (rate per thousand	d) <sup>a</sup> 35 (1.6)	572 (1.9)	376 (2.6)	from 148 (2.8)
Adjusted HR <sup>b</sup>	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2
<sup>a</sup> Rates are per 1000 ongoing	g pregnancies at 20 weeks (early-	onset HELLP syndrome)	and at 34 weeks gestat	ien (late-onset
syndrome).				nj.com/
<sup>b</sup> HR = hazard ratio, with 95%	6 confidence interval in parenthes	ses, unless otherwise sp	pecified. Adjusted for nu	음 비출parity, mate
chronic diabetes, chronic hy	/pertension, in vitro fertilization, a	antepartum bleeding/he	emorrhage, gestational	않 diabetes, alcoh
substance use, smoking dur	ing pregnancy, prior pregnancy or	utcomes, and multiple §	gestation.	<u>2</u> 4 by g
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		BMJ Open	bmjopen-	Paç
STROBE Statemer	nt—ch	ecklist of items that should be included in reports of observational studies	2023-07913	
	Item No.	Recommendation	S S S No.	Relevant text from manuscript
Title and abstract	1	<ul> <li>(a) Indicate the study's design with a commonly used term in the title or the abstract</li> <li>(b) Provide in the abstract an informative and balanced summary of what was done and what was</li> </ul>	Title page arch 2024. Downloaded from 2-3 htt	"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."
		found	tp://bi	
Introduction			<u></u>	1: (7.04
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	4-39	Lines 85-90
Methods	4		<u> </u>	L: 02.122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6 pri	Lines 92-122 Lines 92-122
Participants	6	<ul> <li>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</li> <li><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</li> <li><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</li> </ul>	28, 2024 by guest. Pro	Lines 92-122
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	N/Acted by copyri	N/A

Page	55 c	of 56
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55 of 56		BMJ Open		bmjopen-:	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modified Give diagnostic criteria, if applicable	ers. 5-	2023-0791	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 gro	31 up	31 on 23 Ma	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-	7 ch	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-	202 7	Lines 92-147
				nloaded from http://bmjopen.bmj.com/ on April 28, 2024 by guest. Protected I	
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		BMJ Open	/bmjopen-20	Pa
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-791	Lines 123 - 147
Statistical	12	(a) Describe all statistical methods, including those used to control for confounding	<u></u> 6-7 ο	Lines 123 – 147
methods		(b) Describe any methods used to examine subgroups and interactions	 6-7ស្ត	Lines 123 – 147
		(c) Explain how missing data were addressed	 6-7 ≦	Lines 123 - 147
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	N/AS	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	202	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	24. Dow	
		(e) Describe any sensitivity analyses	6-7 g	Lines 123 - 147
Results			Ided	
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 m ht	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 1	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-88	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		
		Cross-sectional study—Report numbers of outcome events or summary measures	28,	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	8-9N	Lines 165-212
		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were	4 by	
		included	gue	
		(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	N/AQ	
		period	ecte	
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Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	10 07	Lines 213-216
Discussion			913	
Key results	18	Summarise key results with reference to study objectives	11 g	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- <b>13</b>	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-ff202	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-5	Lines 280-307
Other informat	ion		own	
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	Titl⊗pago	e
Note: An Explar	nation	and Elaboration article discusses each checklist item and gives methodological background and published	d exampies of	transparent reporting. The STROB
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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 in British Columbia, Canada.

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-079131.R2
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2024
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<b>Primary Subject Heading</b> :	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Obesity, EPIDEMIOLOGY, OBSTETRICS





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3 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-
8 9		
10		
11	3	based retrospective conort study in British Columbia, Canada.
12		
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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21 22 23 24	22	Work: 604-875-3015; Cell: 778-513-1648; Email: liqing.wang@bcchr.ca
24 25 26	23	
27 28 29	24	Abstract
30 31 32 33	25	Background: Obesity increases risk of pre-eclampsia, but the association with
34 35 36	26	hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is
37 38 39 40	27	understudied.
40 41 42 43	28	Objective: To examine the association between pre-pregnancy body-mass-index (BMI)
44 45 46	29	and HELLP syndrome, including early- vs. late-onset disease.
47 48 49 50	30	Study Design: A retrospective cohort study using population-based data.
51 52 53	31	Setting: British Columbia (BC), Canada, 2008/09-2019/20.
54 55 56 57	32	<b>Population:</b> All pregnancies resulting in live births or stillbirths at $\geq 20$ weeks' gestation.
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1		3
2 3 4		Pre-pregnancy bivit and early- and late-onset HELLP syndrome
5 6 7	33	Methods: BMI categories (kg/m <sup>2</sup> ) included: underweight (<18.5), normal (18.5-24.9),
8 9 10 11	34	overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP
12 13 14	35	syndrome (<34 vs. $\geq$ 34 weeks, respectively) were calculated per 1000 ongoing
15 16 17 18	36	pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to
19 20 21	37	assess the associations between risk factors (e.g., BMI, maternal age and parity) and
22 23 24 25	38	early- vs late-onset HELLP syndrome.
26 27 28	39	Main outcome measures: Early- and late-onset HELLP syndrome.
29 30 31 32	40	Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases
33 34 35	41	among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI,
36 37 38 39	42	overweight and obese categories, respectively. Overall, gestational age-specific rates of
40 41 42	43	HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal
43 44 45 46	44	BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard
40 47 48 49	45	ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP
50 51 52 53 54 55 56 57 58 59	46	syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	47	hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also
8 9 10	48	showed differing AHRs between early- vs. late-onset HELLP syndrome.
12 13 14	49	Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the
15 16 17	50	association is stronger with early-onset HELLP syndrome. Associations with early- and
18 19 20 21	51	late-onset HELLP syndrome differed for some risk factors, suggesting possible
22 23 24	52	differences in etiologic mechanisms.
25 26 27 28	53	Strengths and limitations of this study
29 30 31	54	We were able to describe gestational age-specific incidence of HELLP
32 33 34	55	syndrome, based on population data on all pregnancies.
35 36 37 38	56	The population-based design coupled with detailed information about
39 40 41	57	demographic, behavioural and clinical factors allowed robust adjustment for
42 43 44 45	58	possible confounding.
46 47 48	59	• We did not have detailed information on laboratory values used for the diagnosis
49 50 51 52	60	of HELLP syndrome and therefore we were not able to estimate the severity of
53 54 55 56	61	HELLP syndrome.
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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2		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
3		
4 5	~~	
6	62	• We did not have information about race/ethnicity, socio-economic status (SES)
7		
8	63	and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome
9 10	05	
11		
12	64	<ul> <li>Approximately 25% of women had missing information about BMI, and we used</li> </ul>
13		
14 15		
16	65	multiple imputation methods to address this limitation.
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19 20	66	
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23	67	Key words
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25 26	60	I have the structure of a second second second second sections and second second second second second second se
27	68	Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity,
28		
29	60	pro prograncy counceling, eticlogy, adverse prograncy outcome, RML HELLP
30	09	pre-pregnancy counseling, ellology, adverse pregnancy outcome, bivil, TELLP
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33	70	syndrome
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30 37	71	Word count: 3036
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1 2 3		7 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	92	commonly viewed as a form of severe PE.(9) While the distinction between early- and
8 9 10	93	late-onset PE and the difference in the associations between pre-pregnancy obesity and
11 12 13 14	94	these conditions has been established, such differences have not been studied with
15 16 17	95	regard to HELLP syndrome.
18 19 20 21	96	Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–
22 23 24	97	15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the
25 26 27 28	98	proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The
29 30 31	99	prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18)
32 33 34 35	100	and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in
36 37 38	101	high income countries, the association between maternal pre-pregnancy body-mass-
39 40 41 42	102	index (BMI) and HELLP syndrome has not been adequately assessed in a large
43 44 45	103	population-based study to date.
46 47 48 49	104	We carried out a population-based, retrospective cohort study to examine the
50 51 52	105	association between maternal pre-pregnancy BMI and HELLP syndrome and to assess
53 54 55 56 57 58 59	106	differences in this association in early- vs late-onset HELLP syndrome. We

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	ō
4 5 6 7	107	hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this	
8 9 10	108	relationship may be different in early- compared with late-onset disease. In additional	
11 12 13 14	109	analyses, we examined other risk factors for HELLP syndrome in terms of their	
15 16 17	110	association with early- vs late-onset HELLP syndrome.	
18 19 20 21	111	Materials and Methods	
22 23 24	112	Data sources and study population	
25 26 27 28	113	The study included all live births and stillbirths at ≥20 weeks' gestation in British	
29 30 31	114	Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from	ก
32 33 34 35	115	the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes	
36 37 38	116	information on >99% of births in BC, with detailed data on maternal demographic	
39 40 41 42	117	characteristics, prenatal care, pregnancy complications, labor and delivery	
43 44 45	118	characteristics and neonatal outcomes. Each record, abstracted from medical charts (o	or
46 47 48 49	119	midwives' notes), includes up to 25 International Classification of Diseases, 10 <sup>th</sup> Edition	١,
50 51 52	120	Canadian version (ICD-10-CA) codes for diagnoses related to the delivery	
53 54 55 56 57	121	hospitalization. Chart abstraction is standardized and conducted by trained personnel,	
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			9
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	5
5 6 7	122	and data quality is routinely assessed. Prior validation studies showed high accuracy of	F
8 9 10 11 12	123	collected information on labor and delivery.(21)	
13 14 15	124	Pre-pregnancy BMI and HELLP syndrome	
16 17 18 19	125	Pre-pregnancy weight and height were based on maternal self-report or health care	
20 21 22	126	provider assessment at ≤11 weeks' gestation.(22) BMI was classified as follows (in	
23 24 25 26	127	kg/m <sup>2</sup> ): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese	
27 28 29	128	(≥30.0).(23) The primary outcome of this study was a physician diagnosis of HELLP	
30 31 32 33	129	syndrome documented in the medical chart, and abstracted and recorded in the	
34 35 36	130	BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee	
37 38 39 40	131	classification criteria, namely lactate dehydrogenase $\geq$ 600 IU/I, liver transaminases	
41 42 43	132	(aspartate aminotransferase and alanine aminotransferase) elevated more than twice	
44 45 46 47	133	the upper limit of normal, and a platelet count <100,000/ $\mu$ I (109/I).(24) Early- and late-	
48 49 50	134	onset HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks	
51 52 53 54 55 56 57 58 59	135	and ≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to	

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5	136	ascertain gestational age, and the last menstrual period estimate of gestational age was
6 7 8		
9 10 11	137	used for those without early pregnancy ultrasound information.
12 13	138	Covariates
15 16 17	139	In addition to BMI, we examined the association between maternal age, nulliparity, pre-
19 20 21	140	existing diabetes, chronic hypertension, <i>in vitro</i> fertilization (IVF) conception, multiple
22 23 24 25	141	gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance
26 27 28	142	use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol
29 30 31	143	use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as
32 33 34 35	144	potential confounders; all these factors are known to be associated with HELLP
36 37 38	145	syndrome.(25) Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic
39 40 41 42	146	conditions and pregnancy complications were identified using ICD-10 codes or data
43 44 45	147	fields abstracted from medical charts to the BCPDR (Table A.1).
46 47 48 49	148	Statistical analyses
50 51 52	149	The rates of HELLP syndrome per 1000 deliveries were compared between women in
53 54 55 56 57 58	150	each BMI category. Complete case analyses were performed for individuals with known
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		11
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	151	BMI. The association between pre-pregnancy BMI and HELLP syndrome was first
8 9 10	152	expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained
11 12 13 14	153	from a Cox model without adjustment for other risk factors.
15 16 17	154	Gestational age-specific rates of HELLP syndrome were compared between
18 19 20 21	155	women in the various BMI categories, using undelivered pregnancies at each
22 23 24	156	gestational week as the denominator. These rates were plotted, and splines with 95%
25 26 27 28	157	confidence intervals were fitted by the generalized additive model ("gam") smoothing
29 30 31	158	method. Cox models with interaction terms between pre-pregnancy BMI categories and
32 33 34 35	159	gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain
36 37 38	160	crude HRs and 95% Confidence Intervals (CIs). This analysis was carried out to assess
39 40 41 42	161	whether gestational age at onset modified the association between BMI and HELLP
43 44 45	162	syndrome.
46 47 48 40	163	In multivariable analyses, Cox models were also used to adjust for covariates
50 51 52	164	(listed above) and to also examine their associations with early- vs late-onset of HELLP
53 54 55 56	165	syndrome using interaction terms. We did not assess early- vs late-onset of HELLP
57 58 59		

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1 2		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
3 4 5	166	syndrome interactions with risk factors including alcohol use and prior adverse birth
6 7 8		
9 10 11	167	outcomes due to a low number of women with HELLP syndrome in these categories,
12 13 14	168	but adjusted for them in the model as potential confounders.
15 16 17 18	169	Sensitivity analyses included multiple imputations for missing BMI values based
19 20 21	170	on a multiple imputation procedure using SAS statistical software (PROC MI).(26)
22 23 24 25	171	Variables included in the imputation were those also included in the regression
26 27 28	172	analyses. Ten imputed datasets were created, with the final results obtained using
29 30 31 32	173	Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were
33 34 35	174	compared with the primary analyses.
36 37 38 39	175	All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary,
40 41 42	176	NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British
43 44 45 46	177	Columbia/Children's and Women's Hospital and Health Centre of British Columbia
40 47 48 49	178	Research Ethics Board (#H20-03985).
50 51 52 53 54 55 56 57 58	179	Patient and Public Involvement
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		13 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	180	Neither patients nor the public were involved in the design, or conduct, or reporting, or
8 9 10	181	dissemination plans of our research. We used only de-identified information and the
12 13 14	182	need for patient's consent was waived.
15 16 17	183	
18 19 20 21	184	Results
22 23 24	185	Study population
25 26 27 28	186	Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1,
29 30 31	187	2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational
32 33 34 35	188	age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The
36 37 38	189	study population for the primary analyses included 391,941 pregnancies, after exclusion
39 40 41 42	190	of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP
43 44 45	191	syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).
46 47 48 49	192	The proportion of women who were in underweight, normal BMI, overweight and
50 51 52	193	obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively.
53 54 55 56 57 58 59	194	Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	195	(stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational
8 9 10	196	diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women
11 12 13 14	197	with overweight and obesity compared with women with normal BMI (Table 1).
15 16 17	198	Nulliparity and ultrasound diagnosed fetal growth restriction were observed more
18 19 20 21	199	frequently in the underweight group. Substance use and smoking during pregnancy
22 23 24	200	were more frequent in underweight, overweight, and obese groups compared with
25 26 27 28	201	women with normal BMI.
29 30 31	202	
32 33 34 35	203	Unadjusted analyses for pre-pregnancy BMI
36 37 38	204	The rates of HELLP syndrome in women in underweight, normal, overweight, and
39 40 41 42	205	obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table
43 44 45	206	2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and
46 47 48 49	207	obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90),
50 51 52 53 54 55 56 57	208	respectively, compared with women who had normal BMI (Table A.2).
58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	209	The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2
7 8 9 10	210	(n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation,
11 12 13	211	respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks
15 16 17	212	(75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older
18 19 20 21	213	maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation,
22 23 24	214	bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance
25 26 27 28	215	use and smoking were higher among women with early-onset vs. late-onset HELLP
29 30 31	216	syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity,
32 33 34 35	217	IVF conception, and alcohol use were higher among women with late-onset HELLP
36 37 38	218	syndrome (Table A.3).
39 40 41 42	219	The rates of late-onset HELLP syndrome were higher than early-onset HELLP
43 44 45	220	syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous
46 47 48 40	221	women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal
50 51 52	222	death, IVF conception, multiple gestation, alcohol use and substance use also had
53 54 55 56	223	higher rates of late-onset than early-onset HELLP syndrome. Women with multiple
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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4 5 6 7	224	gestation had highest rate of HELLP syndrome, followed by those with chronic
8 9 10	225	hypertension.
11 12 13 14	226	Differences in gestational age-specific incidence rates of HELLP syndrome by
15 16 17	227	BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-
18 19 20 21	228	age specific rates).
22 23 24	229	Gestational age-specific rates of HELLP syndrome increased over the course of
25 26 27 28	230	pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women
29 30 31	231	with pre-pregnancy BMI below or above normal values but not among those with normal
32 33 34 35	232	BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP
36 37 38	233	syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and
39 40 41 42	234	2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These
43 44 45	235	HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP
46 47 48 49	236	syndrome, respectively (Table A.2).
50 51 52	237	
53 54 55 56 57	238	Adjusted analyses
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1		17
2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	239	The associations did not change substantially after adjusting for other risk factors (Table
8 9 10	240	3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on
11 12 13 14	241	HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly
15 16 17	242	associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP
18 19 20 21	243	syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).
22 23 24	244	Adjusted hazard ratios (AHR) for each risk factor calculated separately for early-
25 26 27 28	245	vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly
20 29 30 31	246	associated with HELLP syndrome included overweight, obesity, advanced maternal age
32 33 34	247	(≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation,
36 37 38	248	and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse
39 40 41	249	association with HELLP syndrome. IVF conception was a risk factor for late-onset but
42 43 44 45	250	not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum
46 47 48	251	bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP
49 50 51 52	252	syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation
53 54 55 56 57 58	253	(p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage

59

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	254	(p=0.011) differed significantly in their associations with early versus late-onset HELLP
8 9 10	255	syndrome (p-values for interaction).
11 12 13 14	256	Sensitivity analyses
15 16 17	257	Women with missing BMI were not substantially different from women with known BMI
18 19 20 21	258	(Table A.5); and the results were not appreciably changed after the analyses were
22 23 24	259	repeated using imputed BMI values (Table A.6).
25 26 27 28	260	
29 30 31	261	Discussion
32 33 34 35	262	Main findings
36 37 38	263	To our knowledge, this is the largest contemporary study examining the association
39 40 41 42	264	between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset
43 44 45	265	disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after
46 47 48 49	266	34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially
50 51 52	267	lower than that of late-onset HELLP syndrome. Women in overweight or obese groups
53 54 55 56	268	were at elevated risk for developing HELLP syndrome. Obesity was more strongly
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		1
1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	269	associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our
8 9 10	270	study showed that chronic hypertension, bleeding before 20 weeks' gestation and
11 12 13 14	271	antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP
15 16 17	272	syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP
18 19 20 21	273	syndrome.
22 23 24	274	Interpretation in the context of scientific literature
25 26 27 28	275	The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the
29 30 31	276	previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-
32 33 34	277	2016.(25) Prior studies describing the association between pre-pregnancy obesity and
36 37 38	278	HELLP syndrome are sparse and results vary. In a retrospective cohort study from a
39 40 41	279	single tertiary hospital in the United States (n=434), Martin et al. found that maternal
42 43 44 45	280	weight was not associated with HELLP syndrome.(29) Similarly, a case-control study
46 47 48	281	(n= 129 cases and 476 controls) found no association between obesity and HELLP
49 50 51 52	282	syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases
53 54 55	283	and 601 controls) showed that pre-pregnancy BMI was associated with PE but not
57 58 59		
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	284	HELLP syndrome and suggested that PE and HELLP may have different
8 9 10	285	pathophysiology.(12) In contrast, a population-based cohort study from Norway
11 12 13 14	286	(n=418,897) found that pre-pregnancy BMI ≥30kg/m <sup>2</sup> was associated with HELLP
15 16 17	287	syndrome in the first but not the second pregnancy.(9) However, in that study, only 25%
18 19 20 21	288	of women with a first pregnancy and 30% of women with their second pregnancy had
22 23 24	289	information on BMI. More recently, a population-based study from Canada
25 26 27 28	290	(n=1,078,323) showed that obesity documented in medical charts was a risk factor for
29 30 31	291	HELLP syndrome,(31) however, obesity rates were underestimated and information on
32 33 34 35	292	BMI was not available, precluding more detailed analyses.
36 37 38	293	While PE is typically recognized as early- vs late-onset disease (before vs $\ge$ 34
39 40 41 42	294	weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A
43 44 45	295	prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is
46 47 48 49	296	a stronger risk factor for late-onset PE than early-onset PE.(15) That study also
50 51 52	297	demonstrated a correlation between increased prevalence of maternal obesity in
53 54 55 56	298	parallel with late-onset PE during the 18-year period, while the incidence of early-onset
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	21 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
299	PE stayed relatively constant.(15) In contrast, our study shows a stronger association
300	between overweight/obesity and early-onset HELLP syndrome compared with late-
301	onset HELLP syndrome. This suggests varying pathophysiological pathways between
302	PE and HELLP syndrome or additional obesity-related pathophysiology associated with
303	PE that leads to liver damage at earlier gestation, for instance, obesity-associated
304	steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age
305	cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia.
306	However, our data suggest an increase in gestational age-specific rates after 28 weeks'
307	gestation in women with obesity and after 30 weeks' gestation in women without
308	obesity. A previous study showed a high proportion of HELLP syndrome cases
309	occurring between 27 and 37 weeks, (33) which indicates potential dissimilarities with
310	early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk
311	factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-
312	onset disease. It is worth mentioning that the known inverse association between
	299 300 301 302 303 304 305 306 307 308 307 308 309 310 311 311

1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
- 5 6 7	313	smoking and PE(6) was also observed in HELLP syndrome in our study, and this
8 9 10 11	314	warrants further investigation.
12 13 14	315	Clinical and research implications
15 16 17 18	316	Our findings show that increases in gestational age-specific rates of HELLP syndrome
19 20 21	317	vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in
22 23 24 25	318	women who were in the underweight, overweight and obese categories, but continued
25 26 27 28	319	increasing in women with normal BMI. This could be due to higher rates of medically
29 30 31	320	indicated early-term deliveries in groups with low or high BMI, which has been shown to
32 33 34 35	321	reduce maternal morbidity compared with expectant management.(34) It is possible that
36 37 38	322	women whose pre-pregnancy BMI was below and above normal range were more likely
39 40 41 42	323	to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and
43 44 45	324	therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal
46 47 48 49	325	and infant outcomes. However, further research is needed to confirm this hypothesis. In
50 51 52	326	addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks'
53 54 55 56 57 58	327	gestation and antepartum bleeding/hemorrhage were more strongly associated with
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		22
1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	328	early- onset HELLP syndrome, while multiple gestation was more strongly associated
8 9 10 11	329	with late-onset HELLP syndrome. The association between bleeding at <20 weeks
12 13 14	330	gestation and early-onset HELLP syndrome is novel. Such bleeding can be caused by
15 16 17 18	331	abnormal placental conditions (e.g., abnormal implantation and associated bleeding),
19 20 21	332	which may play a role in the development of HELLP syndrome. These findings are
22 23 24	333	exploratory and require confirmation by other studies. However, they raise the intriguing
25 26 27 28	334	possibility that determinants of HELLP syndrome (such as antepartum bleeding) have
29 30 31	335	different associations with early and late onset HELLP syndrome depending on whether
32 33 34 35	336	they occur at <20 weeks or at $\ge$ 20 weeks' gestation. In our study, the association
36 37 38	337	between antepartum bleeding at $\geq$ 20 weeks' gestation and HELLP syndrome (which
39 40 41 42	338	could have been explained as being a consequence of HELLP syndrome causing
43 44 45	339	placental abruption) was not significant in adjusted models.
46 47 48 49	340	Strengths and limitations
50 51 52	341	The strengths of this study include its population-based design coupled with detailed
53 54 55 56 57 58 59	342	information about demographic, behavioural and clinical factors that allowed for robust

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1 2 3 4		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
5 6 7	343	adjustment for possible confounding. We had a large enough sample to provide precise
8 9 10	344	estimates for associations with HELLP syndrome, a rare outcome.
12 13 14	345	This study also has several limitations. First, we did not have detailed information
15 16 17	346	on laboratory values important for the diagnosis of HELLP syndrome and therefore we
18 19 20 21	347	were not able to estimate the severity of HELLP. We assumed that the diagnosis of
22 23 24	348	HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal
25 26 27 28	349	condition. However, in milder cases, expectant management with close observation
29 30 31	350	may have led to a delay between the diagnosis and delivery, especially at very preterm
32 33 34 35	351	gestation. As a result, incidence of early-onset HELLP syndrome may have been
36 37 38	352	underestimated in our study. However, we do not expect a large inaccuracy in this
39 40 41 42	353	regard because HELLP syndrome is considered a potentially life-threatening condition
43 44 45	354	and delivery is typically not delayed. Second, we did not have information about
46 47 48 49	355	race/ethnicity, socio-economic status (SES) and prior history of pregnancy with
50 51 52	356	PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding
53 54 55 56	357	in the assessments of the relation between BMI and HELLP syndrome. However, we
57 58 59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3		25 Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	358	adjusted for several possible confounders and did not observe changes in the
8 9 10	359	association between BMI and HELLP syndrome, suggesting that our results are robust.
11 12 13 14	360	Third, pre-pregnancy BMI was largely self-reported, which may have led to some
15 16 17	361	misclassification. Several validation studies have shown relatively good accuracy of
18 19 20 21	362	self-reported weight and height for epidemiological studies,(35–37) suggesting that a
22 23 24	363	large misclassification bias is unlikely. A systematic review of BMI self-report
25 26 27 28	364	misclassification showed minimal influence on associations between BMI and
29 30 31	365	pregnancy outcomes.(38)
32 33 34 35	366	Approximately 25% of women had missing information about BMI. These women
36 37 38	367	were relatively similar to those with known BMI and sensitivity analyses using imputed
39 40 41 42	368	BMI values yielded results almost identical to the main analyses. Lastly, the analyses
43 44 45	369	examining differences between early- and late-onset HELLP and risk factors other than
46 47 48 49	370	BMI were exploratory, and further studies are required to confirm our findings.
50 51 52	371	
53 54 55 56 57	372	Conclusions
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	373	Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk
8 9 10	374	factor for HELLP syndrome. However, contrary to the documented association between
11 12 13 14	375	BMI and PE, with obesity being associated more strongly with late-onset than early-
15 16 17	376	onset PE, our study showed that obesity was more strongly associated with early-onset
18 19 20 21	377	than with late-onset HELLP syndrome. This suggests potentially different underlying
22 23 24	378	pathophysiology for the various hypertensive disorders of pregnancy. Our findings can
25 26 27 28	379	help maternity care providers with regard to pre-pregnancy counselling. Clinicians can
29 30 31	380	better identify women who may benefit from obstetric intervention, as the risk of HELLP
32 33 34 35	381	increases at late pre-term gestation in all women and continues to increase at term and
36 37 38	382	post-term gestation in women with normal pre-pregnancy BMI. More research on the
39 40 41 42	383	gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the
43 44 45	384	underlying causes of HELLP syndrome.
46 47 48 49	385	
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1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome	27			
4 5 6 7	386	Disclosure				
7 8 9 10	387	The authors report no conflict of interest.				
11 12 13 14	388	Disclaimer				
15 16 17 18	389	All inferences, opinions, and conclusions drawn in this publication are those of the				
19 20 21	390	authors, and do not reflect the opinions or policies of Perinatal Services BC.				
22 23 24 25	<ul> <li>22</li> <li>23</li> <li>24</li> <li>291 Author Statement/Contribution to Authorship</li> <li>25</li> </ul>					
26 27 28 29	392	LW and SL were involved in the conception, planning, carrying out and analyzing data	а			
30 31 32 33	393	of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis.				
34 35 36 37	394	LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KS.	J,			
38 39 40 41	395	NR.				
42 43 44	396	Acknowledgement				
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49 50 51 52	398	to the BCPDR database.				
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09	The authors report no conflict of interest.
10	Data Sharing Statement
11	Data may be obtained from a third party and are not publicly available.
12	Ethics Approval Statement
	00 01 02 03 04 05 06 07 08 09 10 11

1 2 3		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
4 5 6 7	413	Ethics approval was obtained from the University of British Columbia/Children's and
8 9 10	414	Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-
11 12 13 14	415	03985).
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	Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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	Pre-pregnancy BMI and ear	ly- and late-c	onset HELLP sy	ndrome	
549	Tables				
550 551	Table 1. Maternal demograp mass-index: British Columb	ohic and clinio ia, 2008/09-2	cal characteristi 019/20ª	cs by pre-preg	nancy body-
		Underweigh	tNormal 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.
	≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.
	Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.
	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 <sup>b</sup>	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 <sup>d</sup>	<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	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
	weeks)				
	Intrauterine Growth Restriction <sup>c</sup>	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.

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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) 2970 (5.5) Substance use 1118 (5.0) 8099 (3.5) 3514 (4.2) 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) 387 (1.7) 28-33 3423 (1.5) 1473 (1.8) 1158 (2.1) 4680 (8.6) 34-36 6142 (7.3) 1620 (7.2) 15119 (6.5) 20076 209831 (90.6) 75017 (89.5) 47448 (87.6) 37-41 (89.7) ≥ 42 207 (0.9) 2263 (1.0) 839 (1.0) 524 (1.0) 552 <sup>a</sup>Data shown as n(%) 553 <sup>b</sup>IVF = in vitro fertilization 554 <sup>c</sup>Ultrasound diagnosed intra-uterine growth restriction (IUGR) <sup>d</sup>Information on cell numbers <5 was suppressed due to confidentiality reasons. 555 Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing 556 pregnancies by maternal demographic and clinical characteristics; British Columbia, 557 558 2008/09-2019/20 Early-onset Late-onset HELLP HELLP Overall syndrome syndrome Pre-pregnancy BMI category 43 (1.9) Underweight 8 (0.4) 35 (1.6) 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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1 2 3		Pre-pregnancy BMI and early- and lat	e-onset HELLP syn	drome	38
4 5		25-34	158 (0.6)	512 (2.1)	670 (2.7)
o 7		≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
8 9		Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
10 11		Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
12 13		Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
14 15		Prior stillbirth /neonatal deatha	<5 (<1.0)	<5 (<1.0)	5 (1.3)
16		IVF conception <sup>b</sup>	19 (1.6)	73 (6.7)	92 (8.0)
17 18		Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
19 20		Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
21 22		Antepartum Bleeding/hemorrhage (≥	20		
23 24		weeks)	15 (2.7)	12 (2.5)	27 (4.8)
25		Alcohol use <sup>a</sup>	<5 (<1.0)	<11 (<2.7)	12 (2.9)
26 27		Substance use	14 (0.9)	25 (1.6)	39 (2.5)
28 29		Smoking	14 (0.5)	36 (1.4)	50 (1.9)
30 31	559	aInformation on cell numbers <5 was	suppressed due to c	confidentiality reas	ons. Other
32 33	560	numbers were suppressed if needed	to avoid back-calcul	ation from the tota	l
34 35	561	<sup>b</sup> IVF = in vitro fertilization			
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### 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 <sup>t</sup>
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)	0.04
Prior stillbirth/neonatal deathc	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception <sup>d</sup>	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.10
Multiple gestation	13.66 (11.06- 16.87)	8.31 (5.59- 12.35)	17.81 (13.89- 22.83)	0.00
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 ( $\geq$ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.01 <sup>,</sup>
Alcohol use <sup>c</sup>	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)	0.16
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.96

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2		Pre-pregnancy BMI and early- and late-onset HELLP syndrome
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5	567	<sup>b</sup> p-value for interaction with early- vs late-onset HELLP syndrome.
6 7	568	°N/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
9 10	505	dW = i a vite factilization
10	570	"IVF = IN VITRO TERTIFIZATION
12	571	
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27 28		
29	576	Figure legend
30 31		
32	577	
33 24	577	
34 35		
36	578	Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category
37 38		
39	579	(Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were
40 41		
42		
43	580	combined. Splines with 95% confidence intervals were fitted by the generalized additive
44 45		
46	581	model ("gam") smoothing method.
47 48		
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50	582	
51 52		
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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1		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 logtransformed 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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	BMJ Open 33 පා ඉ	
Supplementary tables	en-2023-07	
Supplemental Table 1.	. Definitions and sources of variables	
	Definition	Sourc
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPD
NI 11:	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 we get $\mathcal{F}$	ation
Nullipara	in a previous pregnancy.	ВСЬР
	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used.	BCPD
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used;	
	or 'E10', 'E11', 'O245', 'O246', 'O247'	ICD-1
Chronic hypertension	'010','011'	ICD-1
Prior stillbirth	Mother had at least one prior live born infant, who died within the first 28 days of life.	
/neonatal death	Mother had at least one prior stillbirth or intrauterine death documented.	ВСЬР
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPD
	The incremental sequence number of babies born from the current pregnancy. Should be used	
Multiple gestation	with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABO हु जु	BCPD
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Page 46 of 58

	BMJ Open	
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Antepartum bleedin	g g	
< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	
Antepartum		
bleeding or	Sector Mother had any antepartum hemorrhage or bleeding in pregnancy $\geq$ 20 weeks gestation, including	g
hemorrhage ≥ 20	bleeding from cervical polyps.	
weeks	Noaded f	
Intrauterine Growth	Health care provider identified intrauterine growth restriction (IUGR) during the antenatial period.	
Restriction <sup>a</sup>	Baby may or may not be appropriately grown at birth.	
Gestational		
Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	
	Gestational diabetes, insulin dependent.	
Gestational Diabetes	Gestational diabetes, non-insulin dependent.	
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	
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	yright.	
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	Mother used any of the following substances at any time during the current pregnancy $\mathcal{Z}$	
Substance use	لمت heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of ع	BCPDR
	prescription, 'other', or unknown other drug as a risk to the pregnancy. 목	
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, figet ultraso	und
delivery	(<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low	
HELLP syndrome	platelet count)	BCPDR
"Ultrasound diagnos	ed intra-uterine growth restriction (IUGR)	
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		BMJ Open		1 1 36/bmjope
Supplemental Table 2. Rates of HEL	LP syndrome by Body-Ma	ass-Index category ar	nd hazard ratios with 95% o	confidence intervals
	Underweight	Normal BMI	Overweight	G Obese
All pregnancies				23 Mar
N cases (rate per thousand) <sup>a</sup>	43 (1.9)	587 (2.5)	272 (3.2)	♀ 2020 214 (4.0)
Crude HR <sup>b</sup>	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
Early-onset HELLP (< 34 wks)				lloaded
N cases (rate per thousand)ª	8 (0.4)	125 (0.5)	73 (0.9)	from 69 (1.3)
Crude HR <sup>b</sup>	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	
Late-onset HELLP (≥ 34 wks)				open.br
N cases (rate per thousand) <sup>a</sup>	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR <sup>b</sup>	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	9 ₽ 1.42 (1.17-1.71)
Rates are per 1000 ongoing pregn	ancies at 20 weeks (early	y-onset HELLP) and a	at 34 weeks gestation (late	-onset HELLP).
HR = hazard ratio, with 95% confi	dence interval in parenth	ieses, unless otherw	ise specified	24 by g
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upplemental Table 3. Maternal 008/09-2019/20ª	demographic and clinica	<sup>.</sup> - vs late-onset HELLP syn	ndrome; British Columbia	
	Early-onset HEL	LP Late-onset HELLP		n 23 Ma
	n =275	n = 841		rch 2024
Pre-pregnancy BMI category	0		-	Downl
Underweight	8 (2.9)	35 (4.2)		oaded f
Normal weight	125 (45.5)	462 (54.9)		
Overweight	73 (26.6)	199 (23.7)		p://bmjo
Obese	69 (25.1)	145 (17.2)		pen.bm
Maternal age (years)				j.com/ c
< 25	30 (10.9)	97 (11.5)		n April
25-34	158 (57.5)	512 (60.9)		28, 202
≥ 35	87 (31.6)	232 (27.6)		4 by gue
Nullipara	188 (68.4)	629 (74.8)		∍st. Prot
Chronic diabetes	6 (2.2)	14 (1.7)		ected b
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Page 51 of 58			BMJ Open
1 2			
- 3 4	Chronic hypertension	19 (6.9)	20 (2.4)
5 6 7	Prior stillbirth /neonatal death <sup>b</sup>	<5 (<1.8)	<5 (<0.5)
8 9 10	IVF conception <sup>c</sup>	19 (6.9)	73 (8.7)
11 12	Multiple gestation	33 (12.0)	91 (10.8)
13 14 15	Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
16 17	Antepartum bleeding/hemorrhage (≥	15 (5.5)	12 (1.4)
18 19 20	20 weeks)		
21 22	Alcohol use <sup>b</sup>	<5 (<1.8)	10 (1.2)
23 24 25	Substance use	14 (5.1)	25 (3.0)
26 27 28	Smoking	14 (5.1)	36 (4.3)
20 29	<sup>a</sup> Data shown as n(%)		51
30 31 32	<sup>b</sup> Information on cell numbers <5 was su	uppressed due to co	nfidentiality reasons.
33 34 35	<sup>c</sup> IVF = in vitro fertilization		
36 37			
38 39 40			
41 42			

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Gestational age	Underweight	Normal BMI	Overweight	 Obese
(weeks)	n = 22,392	n = 231,517	n = 83,864	23 Man = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	25/54168 (<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)	<u>ଛ</u> ଡୁ5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	ō 6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	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)	9 전42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	ಜ್ ಜ್ಞ5/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	بة ح 236/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	يَّةٍ 12/15135 (0.79)
imbia, 200/09-2019/20ª				
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	BMI not missing	BMI missing	—	
	n = 391,941	n = 132,536		
ernal age (years)	0			
25	47030 (12.0)	20134 (15.2)		
-34	247268 (63.1)	78660 (59.4)		
35	97643 (24.9)	33742 (25.5)		
ipara	189513 (48.4)	53789 (40.6)		
existing diabetes	2397 (0.6)	913 (0.7)		
onic hypertension	2847 (0.7)	890 (0.7)		
r stillbirth /neonatal death	3794 (1.0)	1734 (1.3)		
conception <sup>b</sup>	11549 (3.0)	3877 (2.9)		
tiple gestation				
vins	5806 (1.5)	2478 (1.9)		
/1115	2006 (1.2)	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 <sup>c</sup>	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)

 <sup>b</sup>IVF = in vitro fertilization

 $^{\rm c}{\rm Ultrasound}$  diagnosed intra-uterine growth restriction (IUGR)

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Page	55	of	58
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Early-onset HELLP (< 34 wks)         N cases (rate per thousand) <sup>a</sup> 8 (0.4)       164 (0.5)       137 (0.9)         Adjusted HR <sup>b</sup> 0.76 (0.43-1.33)       Ref       1.54 (1.19-2.00)         Late-onset HELLP (≥ 34 wks)       0.96 (0.51-1.8)       Ref       1.24 (0.92-1.66)         Adjusted HR <sup>b</sup> 0.96 (0.51-1.8)       Ref       1.24 (0.92-1.66)         Particular are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (Insyndrome).       1.4 <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nullpart chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational data be substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.       9	Ohese	Overweight 3	Normal BMI	Underweight	
Early-onset HELLP (< 34 wks)       8 (0.4)       164 (0.5)       137 (0.9)       71         Adjusted HR <sup>b</sup> 0.76 (0.43-1.33)       Ref       1.54 (1.19-2.00)       2.0         Late-onset HELLP (≥ 34 wks)	Obese	S S S S S S S S S S S S S S S S S S S		onderweight	
N cases (rate per thousand)a8 (0.4)164 (0.5)137 (0.9)11Adjusted HRb0.76 (0.43-1.33)Ref1.54 (1.19-2.00)2.0Late-onset HELLP (≥ 34 wks)N cases (rate per thousand)a35 (1.6)572 (1.9)376 (2.6)1.4Adjusted HRb0.96 (0.51-1.8)Ref1.24 (0.92-1.66)1.4aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (It syndrome)bHR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulfibration, antepartum bleeding/hemorrhage, gestational data substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestationPage Substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation		Marc			Early-onset HELLP (< 34 wks)
Adjusted HR <sup>b</sup> 0.76 (0.43-1.33)       Ref       1.54 (1.19-2.00)       02.0         Late-onset HELLP (≥ 34 wks)       N cases (rate per thousand) <sup>a</sup> 35 (1.6)       572 (1.9)       376 (2.6)       14         Adjusted HR <sup>b</sup> 0.96 (0.51-1.8)       Ref       1.24 (0.92-1.66)       1.24 <sup>a</sup> Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (h       1.24       1.24         syndrome). <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for number chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabete substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.       Weeks the substance use, smoking during pregnancy prior pregnancy outcomes, and multiple gestation.       Weeks the substance use, smoking during pregnancy prior pregnancy outcomes, and multiple gestation.	71 (1.3)	137 (0.9) 2024	164 (0.5)	8 (0.4)	N cases (rate per thousand) <sup>a</sup>
Late-onset HELLP (≥ 34 wks) N cases (rate per thousand) <sup>a</sup> 35 (1.6) 572 (1.9) 376 (2.6) 14 Adjusted HR <sup>b</sup> 0.96 (0.51-1.8) Ref 1.24 (0.92-1.66) 1.4 <sup>a</sup> Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (k syndrome). <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for number chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational does substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.	2.06 (1.53	1.54 (1.19-2.00)	Ref	0.76 (0.43-1.33)	Adjusted HR <sup>b</sup>
N cases (rate per thousand) a       35 (1.6)       572 (1.9)       376 (2.6)       14         Adjusted HRb       0.96 (0.51-1.8)       Ref       1.24 (0.92-1.66)       1.4         aRates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (h       1.4         syndrome).       b       HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for null parentheses, unless otherwise specified. Adjusted for null parentheses, unless otherwise specified. Adjusted for null parentheses substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.       360		oaded f			Late-onset HELLP (≥ 34 wks)
Adjusted HR <sup>b</sup> 0.96 (0.51-1.8)       Ref       1.24 (0.92-1.66)       1.24 <sup>a</sup> Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (lasyndrome).       * <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for null parentheses, unless otherwise specified. Adjusted for null parentheses, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.       Weeks Week	148 (2.8)	376 (2.6)	572 (1.9)	35 (1.6)	N cases (rate per thousand) <sup>a</sup>
<sup>a</sup> Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (h syndrome). <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for null par chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.	1.46 (1.03	1.24 (0.92-1.66)	Ref	0.96 (0.51-1.8)	Adjusted HR <sup>b</sup>
syndrome). <sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulpar chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabet substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.	n (late-ons	d at 34 weeks gestatie	HELLP syndrome)	es at 20 weeks (early-ons	<sup>a</sup> Rates are per 1000 ongoing pregnar
<sup>b</sup> HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for null parentheses, unless otherwise specified. Adjusted for null parentheses, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.		mj.com/ o			syndrome).
chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabet substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.	parity, mai	fied. Adjusted for nul	nless otherwise sp	e interval in parentheses,	<sup>b</sup> HR = hazard ratio, with 95% confide
substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.	abetes, alc	ର Sorrhage, gestational dia ରି	artum bleeding/he	, in vitro fertilization, ante	chronic diabetes, chronic hypertensi
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STROBE Statemen	nt—ch	ecklist of items that should be included in reports of observational studies	2023-07913	
	Item No.	Recommendation	S Page N No.	Relevant text from manuscript
Title and abstract	1	<ul> <li>(a) Indicate the study's design with a commonly used term in the title or the abstract</li> <li>(b) Provide in the abstract an informative and balanced summary of what was done and what was</li> </ul>	Title page rch 2024. Downloaded from 2-3	"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."
		found	http://b	
Introduction			<u></u>	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-58	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	<u>4-5 g</u>	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	<u>5-6 2</u>	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6 April :	Lines 92-122
Participants	6	<ul> <li>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</li> <li>Case-control study—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</li> <li>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</li> </ul>	28, 2024 by guest. Pro	Lines 92-122
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	N/Acted by copyrigh	N/A

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Page	57	of	58
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## BMJ Open

7 of 58		BMJ Open	bmjopen-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	5-791	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 on 23 Ma	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7 ch	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-78	Lines 92-147
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		BMJ Open	/bmjopen-24		Pag
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7913	Lines 123 - 147	
Statistical	12	(a) Describe all statistical methods, including those used to control for confounding	6-7 o	Lines 123 – 147	
methods		(b) Describe any methods used to examine subgroups and interactions	6-7 <u>ເ</u>	Lines 123 – 147	
		(c) Explain how missing data were addressed	6-7≦	Lines 123 - 147	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	N/AS		
		Case-control study-If applicable, explain how matching of cases and controls was addressed	202		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	4. Dow		
		(e) Describe any sensitivity analyses	6-78	Lines 123 - 147	
Results		6	ded		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined	7-8 m	Lines 149-164	
		for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	htt		
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164	
		(c) Consider use of a flow diagram	29 3.	Supplemental Figure 1	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164	
		(b) Indicate number of participants with missing data for each variable of interest	7-88	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*	Cohort study—Report numbers of outcome events or summary measures over time	7-8 ⊳	Lines 149-164	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	p ril		
		Cross-sectional study—Report numbers of outcome events or summary measures	,28 ,08		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	8-90	Lines 165-212	
		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were	4 by		
		included	gue		
		(b) Report category boundaries when continuous variables were categorized	5 . <del>S</del> t. –	Lines 105-106	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/AQ		
		period	ecte		
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Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	10 5	Lines 213-216
Discussion			913	
Key results	18	Summarise key results with reference to study objectives	11 g	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss	13-23	Lines 280-307
		both direction and magnitude of any potential bias	Mar	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	11-8	Lines 230-279
		analyses, results from similar studies, and other relevant evidence	2024	
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-5	Lines 280-307
Other informati	on		ownl	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the	Titlepage	
		original study on which the present article is based	ed f	
*Give informatio	n sep	parately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups	s in cohort and	cross-sectional studies.
Note: An Explan	ation	and Elaboration article discusses each checklist item and gives methodological background and published	d exampies of t	ransparent reporting. The STROBE
checklist is best i	ised i	n conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosme	dicine or Ani	als of Internal Medicine at

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