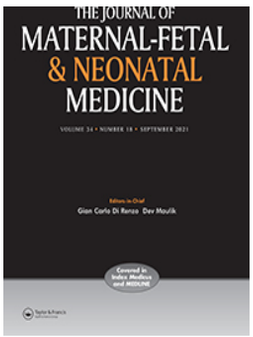

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ORIGINAL ARTICLE

Cardiovascular complications following cesarean section and vaginal delivery: a national population-based study

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ABSTRACT

Introduction: Rates of cesarean section are rising in both developed and developing countries and while pregnancy and cesarean section are established as risk factors for thromboembolism and stroke, large population-based investigations focusing on all types of cardiovascular complication after delivery is missing. The aim was to analyze the risk of severe cardiovascular complications in the post-partum period following delivery by cesarean section. We also had a control group of vaginal deliveries and a reference group with nulliparas.

Materials and Methods: This Swedish population-based study used three national registers between 2005 and 2017 and comprised a total of 1 165 684 individuals. Unselected register data was cross-linked and cardiovascular adverse events were identified by ICD diagnosis codes. 140 128 women (209 391 deliveries) were included in the cesarean group and 614 355 women (973 429 deliveries) in the vaginal control group. The reference group comprised 411 201 age-matched nulliparous women. The primary analysis was the risk of severe cardiovascular complications within 42 days of cesarean section or vaginal delivery. The secondary analysis evaluated risk factors for cardiovascular complications.

Results: In the cesarean section group, 410 (0.20%) had a serious cardiovascular event within 42 days after delivery, and in the vaginal control group the number was 857 (0.09%). The risk of having an adverse cardiovascular event was significantly greater in the cesarean group (OR 2.23, CI 1.98 to 2.51) for all types of cardiovascular events. Risk factors were high BMI, preeclampsia, greater maternal age, tobacco use and acute cesarean delivery.

Conclusions: The absolute numbers on severe maternal morbidity after delivery are low. However, since almost half of the world's population are affected and the frequency of elective cesarean section continues to rise, a doubling of the risk for a severe cardiovascular event within 42 days of delivery is important to consider globally.

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Cesarean section; cardiovascular complications; complications after delivery; deep vein thrombosis; myocardial infarction; pulmonary embolism; stroke

Introduction

Rates of cesarean section are rising in both developed and developing countries [1–5]. When performed for obstetric indications, cesarean section can effectively reduce maternal and perinatal mortality and morbidity. However, there is no evidence showing the benefit of cesarean delivery in the absence of a clear medical indication [6–10].

Cesarean section is considered a safe procedure but may have complications. Both pregnancy and cesarean section entail an increased risk of venous thromboembolism and stroke [8,11–14].

Pregnancy is a hypercoagulable state related to important hemostatic changes, including increase in coagulation factors such as factor VIII, von Willebrand factor and fibrinogen, and a decrease in inhibitors such as protein S [15]. This results in a lower risk for hemorrhage associated with delivery, which is the leading cause of maternal mortality in developing countries [16]. Unfortunately, hypercoagulation also

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leads to an increased risk for cardiovascular events [17–18].

In high-income countries, thromboembolic disease is one of the major cause of maternal mortality [19]. According to a WHO systematic analysis, venous embolism alone is responsible for 13.8% (95% CI, 10.1–22.0) of all maternal deaths in developed countries [16]. Considering most cardiovascular complications and even maternal deaths occur postpartum [20–21], and the highest risk for cardiovascular complication is in the postpartum period [22–23], the influence of mode of delivery on the risk should be further investigated. Several previous studies have attempted to compare the risks for maternal morbidity and mortality after cesarean section versus vaginal delivery, but most focus on the more obvious obstetric complications such as bleeding, uterine rupture and neonatal adverse outcome; all showing more complications after cesarean delivery [24–25]. There are also studies on pregnancy-related cardiovascular complications [18,17], but no large population-based investigation focusing on all types of cardiovascular complication after delivery.

The aim of this study was to estimate cardiovascular complication rates following cesarean section, with vaginal delivery as a control group, using data from national registers. The hypothesis is that the risk for a cardiovascular complication is greater after cesarean section.

Materials and methods

This is an observational population-based study using data from three national registers: the Swedish National Patient Register, the Swedish Medical Birth Register, and Statistics Sweden. Cross-linked unselected data from these registers were used to identify cardiovascular adverse events within 42 days of delivery (generally known as the puerperium and commonly used in this type of study) [26] identified by ICD (International Classification of Disease) diagnosis codes. The study is reported following the STROBE Statement checklist for cohort studies.

The *Swedish National Patient Register*, started in 1964, has full coverage of hospital inpatient admissions (public as well as private) since 1987 and of outpatient visits since 2001. It includes data on all in- and outpatient diagnoses and surgical intervention codes according to the current ICD protocol. The register is validated and only 1% of data regarding inpatient care is currently missing. Primary care patients are not included [27].

The *Swedish Medical Birth Register* was established in 1973 and contains data collected from medical records regarding all pregnancies, deliveries and the neonatal periods. The coverage is almost complete with 97-99% of all deliveries registered. Variables include body mass index (BMI), smoking habits during pregnancy, comorbidity, the mode of delivery, the number of previous deliveries, fetal presentation and medical data regarding the neonate [28,29].

Statistics Sweden is a government agency founded in 1858 with the main aim to collect statistics for decision-making, debate and research. The agency maintains the Swedish Total Population Register, widely used in Sweden to provide matched controls for cohort studies [30].

Each Swedish citizen has a unique personal identification number. This makes it possible to cross-link data from different registers and to follow individuals over time regardless of where in the country they live or receive medical care [31].

The study groups included all women in the Swedish Medical Birth Register who underwent cesarean section or vaginal delivery during the period 2005–2017. The cesarean section group included women who gave birth by cesarean section only and no previous vaginal delivery. The vaginal delivery control group included women who gave birth by vaginal delivery only and no previous cesarean delivery. In the main analyses, every delivery was included, therefore some women occur more than once (Figure 1). A separate subgroup analysis was made with only primiparas. Exclusion criteria were: women with both vaginal and cesarean deliveries; and those with four or more deliveries (the National Board of Health and Security, holder of the registers used in this study, does not approve of including women after four or more deliveries due to the risk of identification). The female nulliparous reference group was completely age-matched to the cesarean section and vaginal delivery groups and derived from the Total Population Register. In this register, there is no data regarding for example comorbidity, smoking habits or Body Mass Index. Cardiovascular diagnoses according to ICD 10 were divided into five groups: deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction; and death (includes all causes of death, not only cardiovascular) (Table 1).

The primary analysis was the risk of severe cardiovascular complications within 42 days of cesarean section. We also analyzed the risk for the vaginal control group and for the nulliparous reference group regarding cardiovascular complications during the whole

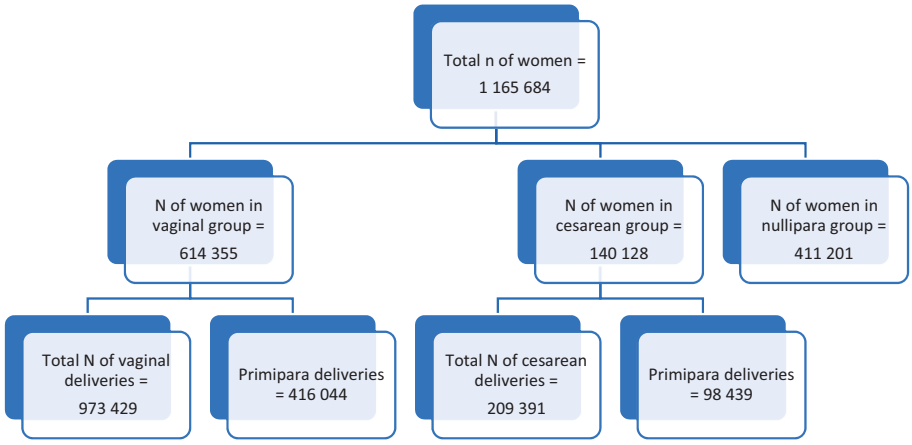

Figure 1. Number of patients studied. The two study groups comprised all women in the Swedish Medical Birth Register who gave birth by one, two or three cesarean sections or vaginal deliveries between 2005 and 2017. The control group consists of age matched nulliparous women from the Total Population Register.

Table 1. ICD-codes used to identify cardiovascular complications. All ICD 10 diagnoses in the study were allocated to 5 diagnosis groups.

ICD10 diagnosis code	1. Deep vein thrombosis	2. Pulmonary embolism	3. Stroke	4. Myocardial infarction	5. Death
I87.1	X				
I80.1-3,9	X				
I74	X				
I81	X				
I82	X				
I26 Pulmonary embolism		X			
O88 Pulmonary embolism		X			
O87.3 Cerebral venous thrombosis			X		
I61 Cerebral hemorrhage			X		
I63 Stroke			X		
O22.5 Cerebral venous thrombosis during pregnancy			X		
I21 Myocardial infarction				X	
O95 Obstetric death					X

study period. Since the nulliparous group have no deliveries, we could not study the first 42 days in this specific analysis but had to include the whole study period.

The secondary analysis determined risk factors for cardiovascular complication.

To identify predictors of a cardiovascular event the study population was divided into subgroups. Maternal age at first delivery was dichotomized into <30 years and ≥ 30 years. Maternal BMI at first antenatal visit was dichotomized into <25 and ≥ 25, which was close to mean BMI for the whole cohort. Infant birth weight was dichotomized into above or below median. Vaginal deliveries were divided into instrumental (mostly vacuum extractor, forceps is extremely rare in Sweden) or noninstrumental delivery. Cesarean sections were divided into acute (after start of labor) or elective (before start of labor) cesarean according to the definition in the register [29]. Unfortunately, the reason for cesarean section could not be derived from our register data. Tobacco means any form of tobacco (snuff or smoking) used at least once during pregnancy.

Patient characteristics are presented as means, or the actual number with percentage. Differences in the results between women who gave birth by cesarean section or vaginal delivery were tested using the Student's t-test or Pearson's Chi^2, as appropriate (Table 2).

The data on the timing of different cardiovascular events (during pregnancy, 0–42 days and >42 days after delivery) are presented graphically.

The association between type of delivery and severe cardiovascular complications within 42 days following birth, were given as Odds ratios (OR).

Multivariate logistic regression analysis was used to identify risk factors associated with severe cardiovascular complications within 42 days following birth.

Table 2. Characteristics of the women giving birth by cesarean or vaginal delivery.

	Cesarean n (%)	Vaginal n (%)	Missing n (%)	*p*-value
Total n of women	140,128	614,355		
Total n of deliveries in each group	209,391	973,429		
Mean age at first delivery (years)	31.3 ± 5.5	29.4 ± 5.3	10	<.001*
Mean infant birthweight (g)	3,400	3,505	1,125	<.001*
Tobacco user	29,161 (22.1)	128,162 (22.0)	39,410 (5.2)	.408†
Primipara	98,881 (71.3)	417,372 (68.8)	0	<.001†
Maternal BMI (Mean)	25.38	24.28	36,802 (4.9)	<.001*
Preeclampsia	5,796 (4.1)	12,423 (2.0)	0	<.001†
Eclampsia	366 (0.3)	243 (0.0)	0	<.001†
Acute Cesarean	81,045 (62.1)			
Instrumental delivery		74,806 (12.2)		
Twins	5,955 (4.2)	4,393 (0.7)	0	<.001†
DVT during pregnancy	118 (0.1)	351 (0.0)		<.001†

*T-test, †Chi2-test.

A second multivariate logistic regression model to identify risk factors was used for those with cesarean section. For both models, adjustments were made for all the risk factors from Table 2. Risk factors without significance were removed until only significant risk factors remained.

All *p*-values and confidence intervals were estimated according to Wald, with 2-tailed *p*-values and with the limit 0.05 as statistically significant. Statistical analyses were made using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics software, version 24 (IBM Corp Armonk, NY, USA).

Ethics approval for this study was granted by the Regional Ethics Committee at Umeå University, Sweden (Dnr 2015-410-31, Dnr 2016-12-32, D.nr: 2019-01533).

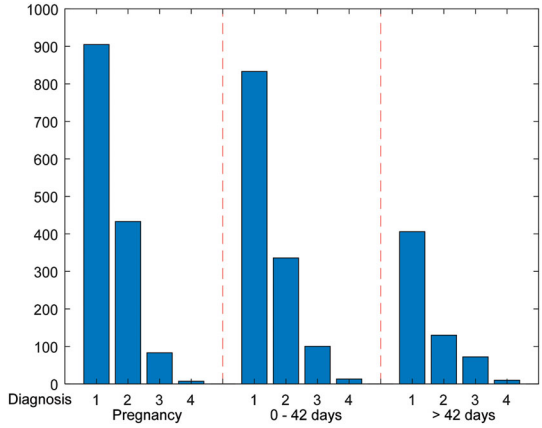

Figure 2. Number of cardiovascular events in relation to delivery. Number of cardiovascular events (y-axis) according to diagnosis group (1-4) and according to time of occurrence (pre- or post-delivery; 0-42 or >42 days; x-axis). 1 = DVT, 2 = Pulmonary Embomolism, 3 = Stroke, 4 = Myocardial infarction

Results

A total of 1 165 684 individuals were included in the study; 140 128 women gave birth by a total of 209 391 cesarean deliveries and 614 355 women in the vaginal group by a total of 973 429 vaginal deliveries between 1st January 2005 and 31st December 2017 in Sweden. The reference group consisted of 411 201 age-matched nulliparous women (Figure 1).

Patient characteristics are presented in Table 2. Women in the cesarean group were almost 2 years older at their first delivery and had a slightly higher BMI. Preeclampsia, eclampsia, and twins were more frequent in the cesarean delivery group and the mean infant weight was lower.

Figure 2 describes the absolute numbers of events for each cardiovascular complication in relation to delivery. Most events occurred during pregnancy or within 42 days of delivery.

Of the 209 391 deliveries in the cesarean group, 410 (0.20%) had a serious cardiovascular event within 42 days after delivery and in the vaginal control group the number was 857 of 973 429 (0.09%). The risk for having an adverse cardiovascular event was significantly higher in the cesarean group (OR 2.23, 1.98–2.51) for all types of cardiovascular event. The most frequent complication was deep vein thrombosis with an incidence of 0.11% after cesarean delivery and 0.06% after vaginal delivery (Table 3a).

In comparison with the reference group of nulliparous women, the risk for any cardiovascular event during the whole study period was higher for women having a cesarean section (OR 1.26, 1.18–1.35, $p < .0001$). However, the risk was lower for women in the vaginal delivery group than in the nulliparous group (OR 0.73, 0.69–0.78, $p < .0001$) (Table 3b).

We also made a separate analysis with only primiparas in Table 4. Even though the cases are fewer in this group, the risk for a serious cardiovascular complication after cesarean delivery is even more enhanced.

In a multivariable model, cesarean section, high BMI, preeclampsia, high maternal age and tobacco

were risk factors for cardiovascular event within 42 days of delivery.

The increased risk after cesarean section remained after adjustment for these other risk factors (Table 5a).

Acute cesarean section had a higher risk for cardiovascular event than elective cesarean section (OR 1.27, 1.03–1.58, $p < .0287$) (Table 5b).

Discussion

This large nationwide population study shows that the risk for a serious cardiovascular complication within 42 days after delivery was more than twice as high after cesarean section compared with vaginal delivery. This was the case not only for all events but also for all five subgroups (DVT, pulmonary embolism, myocardial infarction, stroke and death). The risk was even more pronounced in the group with only primiparas. The fortunately very few cases of myocardial infarction and death makes it impossible to draw any conclusions regarding these diagnoses.

The risk factors for a cardiovascular complication were: cesarean section, high maternal BMI, tobacco use and preeclampsia. Most interesting here are the life-style associated factors; BMI and tobacco use. This illuminates the importance of preventive work regarding women's health that can hopefully, among many other benefits, reduce these complications.

When analysis included the nullipara reference group, the risk for a severe cardiovascular event over the same time period was higher in the nullipara group than in the vaginal group. Since pregnancy and delivery are known risks for cardiovascular events this may seem counterintuitive [17–18]. This may have been due to selection where the group of women giving birth were actually healthier than the much smaller control group of nulliparous women. Thus, the group of nulliparous women comprise not only healthy voluntary childless women and healthy infertile women but also women who cannot, or believed that they should not, have children because of comorbidity, chromosome-abnormalities or heredity. Data to allow the analysis of such details in this group were not available.

The use of nationwide population-based registers with almost full coverage enabled the study of rare cardiovascular events and prevented selection bias. The large number of deliveries gives this study a unique power and to our knowledge, there is no study in this size covering all cardiovascular complications.

Table 3a. Cardiovascular events within 42 days of delivery.

Delivery (n)	n (%)	OR*	CI (95%)	*p*-value
All Cardiovascular Events				
VD (973,429)	857 (0.09)	1		
CD (209,391)	410 (0.20)	2.23	1.98−2.51	<.001
Deep Vein Thrombosis (1)				
VD	598 (0.06)	1		
CD	235 (0.11)	1.83	1.57−2.12	<.001
Pulmonary Embolism (2)				
VD	203 (0.02)	1		
CD	133 (0.06)	2.87	2.33−3.54	<.001
Stroke (3)				
VD	59 (0.01)	1		
CD	41 (0.02)	3.23	2.17−4.82	<.001
Myocardial Infarction (4)				
VD	5	1		
CD	8	7.45	2.44−22.8	<.001
Death (5)				
VD	6	1		
CD	3	2.33	0.58−9.30	.232

Table 3b. Cardiovascular events during total study period.

	N (%)	OR	CI	*p*-value
Event (All)				
Nullipara (411,201)	1981 (0.48)	1		
VD (973,429)	3448 (0.35)	0.73	0.69–0.78	<.001
CD (209,391)	1271 (0.61)	1.26	1.18–1.35	<.001

*Odds ratio. †Confidence interval. Univariable logistic regression analysis showing the association between type of delivery and outcome events within 42 days (3a) and the total number of cardiovascular events in each group (3 b). Some women occur more than once, since separate deliveries were included. When comparing with the nulliparous group, the whole study period had to be included since there are no deliveries in this group.

Table 4. Cardiovascular events within 42days of delivery. Primiparas only.

	Delivery (*n*)	*n* (%)	OR	CI (95%)
All Cardiovascular Events	VD (416,044)	267 (0.064)	1	
	CD (209,391)	159 (0.162)	2.52	2.07−3.07
Deep Vein Thrombosis (1)	VD	187 (0.044)	1	
	CD	94 (0.095)	2.13	1.66−2.72
Pulmonary Embolism (2)	VD	51 (0.012)	1	
	CD	43 (0.044)	3.56	2.38−5.35
Stroke (3)	VD	31 (0.019)	1	
	CD	19 (0.02)	2.59	1.46−4.59
Myocardial Infarction (4)	VD	1	1	
	CD	3	12.68	1.32−121.90
Death (5)	VD	3	1	
	CD	2	2.82	0.47−16.86

Univariable logistic regression analysis showing the association between type of delivery and outcome events within 42days.

Table 5a. Risk factors for cardiovascular events within 42 days of delivery.

Parameter	OR (95%CI)	*p*-value
All Events		
Cesarean	1.98 (1.74−2.24)	<.001
Maternal age*	1.35 (1.19−1.53)	<.001
BMI†	1.93 (1.72−2.17)	<.001
Tobacco	1.19 (1.03−1.37)	.017
Preeclampsia	2.06 (1.58−2.68)	<.001
1. Deep Vein Thrombosis		
Cesarean	1.67 (1.43–1.96)	<.001
Maternal age*	1.36 (1.18–1.58)	<.001
BMI†	1.81 (1.57–2.09)	<.001
DVT during pregnancy	151.5 (102.1–224.6)	<.001
2. Pulmonary Embolism		
Cesarean	2.75 (2.18–3.45)	<.001
BMI†	2.46 (1.95–3.10)	<.001
Preeclampsia	2.72 (1.77–4.17)	<.001
Eclampsia	6.01 (1.48–24.35)	.012
DVT during pregnancy	21.82 (5.39–88.38)	<.001
3. Stroke		
Cesarean	2.16 (1.39–3.38)	<.001
BMI†	1.87 (1.22–2.88)	.004
Tobacco	2.26 (1.46–3.50	<.001
Infant birthweight§	0.50 (0.32–0.78)	.003
Preeclampsia	4.53 (2.37–8.66)	<.001
Eclampsia	27.82 (8.52–90.82)	<.001
4. Myocardial Infarction		
Cesarean	7.45 (2.44–22.35)	<.001

Table 5b. Risk factors for cardiovascular events within 42 days after cesarean delivery only.

Parameter	OR (95 % CI)	*P*-value
All Events		
Acute cesarean	1.27 (1.03–1.58)	.029
Maternal age*	1.32 (1.04–1.67)	.021
BMI†	2.05 (1.65–2.54)	<.001
Infant birthweight§	0.67 (0.54–0.83)	<.001
Eclampsia	5.36 (1.98–14.51)	.001

* ≥ 30 years. † ≥ 25. § Above or below median. A multivariable logistic regression analysis showing the adjusted OR for risk factors for cardiovascular events. Adjusted for all significant risk factors that could be found in Table 2.

The amount of missing data was minimal, which makes generalization of the results feasible.

A limitation of this study is that some cases of coronary dissection might be missed in this study, since this diagnosis is not included. The registers do not include personal history, family history of cardiovascular events or ethnicity, which could have been interesting knowledge. Even though the study design with the national registers makes this population unselected, it includes only Swedish women and might not be applicable in a more low-income setting. Another limitation of the present study is that it was not possible to identify the reason for performing cesarean section - that is, whether this was done for a medical indication or not.

There is no reason to think that the group of women with a cesarean section done without a true medical indication would have any other risk factors for cardiovascular complications than women in the vaginal delivery group, except for the cesarean section itself. However, the group of women who delivered by cesarean section for medical reasons are possibly at higher risk for complication from the beginning (and were therefore planned for a cesarean or needed an acute cesarean). It could also be that other residual confounders not available in the registers influenced our results, for example maternal comorbidities such as diabetes, hypercoagulability, hypertension, cardiac-, renal- and inflammatory disease.

Interestingly, the increased risk for cardiovascular complications after cesarean section remained after adjusting for preeclampsia. It is possible that although adjusting for preeclampsia and other predictors, an overrepresentation of women with a more severe preeclampsia was present in the cesarean delivery group [32].

Even though some of the cardiovascular complications after cesarean section are attributable to a preexisting condition (which leads to the decision to use this approach) and not to the procedure itself, most caesareans are performed due to fetal distress, cephalopelvic disproportion, dystocia or prior cesarean, and not a maternal medical indication [29]. Furthermore, there is no evidence that a cesarean section is safer than a vaginal delivery in the event of comorbidity [9,33] and therefore, women with preexisting morbidity are included in both groups.

Different approaches and study designs have been used in previous studies to try to minimize confounders such as comorbidity, and make the study groups more comparable. Thus, Liu *et al* used cesarean for breach presentation as the surrogate for planned cesarean section, comparing this with vaginal delivery and reported an overall low but increased risk for severe maternal morbidity including cardiac arrest and venous thromboembolism in the cesarean delivery group [34]. Korb *et al*., in a population-based propensity score analysis of severe maternal morbidity, reported that cesarean section had a higher risk for severe acute maternal morbidity [24].

The optimal way of studying risks with cesarean section would be to randomize two identical groups of women to cesarean section or vaginal delivery. However, not only would this be ethically doubtful but also organizationally difficult as a planned cesarean not seldom instead becomes a preterm vaginal delivery or an acute cesarean, just as a planned vaginal delivery may convert into an acute or subacute cesarean section. It is not surprising therefor that no RCT exists in this area [10].

In this study, acute cesarean sections had a higher risk for cardiovascular complication than elective cesarean sections. There is reason to assume that the indication for an emergency cesarean section is in most cases justified and that the alternative holds greater risk for both mother and child. However, it is important to aim to perform acute as well as elective cesareans for legitimate reasons to reduce complications.

Conclusion

Our study shows a doubled risk for a cardiovascular complication after cesarean section compared to vaginal delivery with high BMI and tobacco use as two preventable risk factors. This shows that the important work to improve women's health world-wide must be enhanced. Although the absolute numbers on severe maternal morbidity after delivery are low in Sweden, the world-wide frequency of elective cesarean sections continue to rise, and is as high as 30–50% in several countries. Therefore, an increased risk of severe cardiovascular complications is important to consider and further research from different settings globally would be of great value.

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