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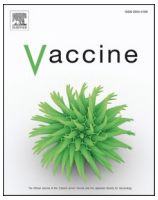

Individual and familial factors associated with mRNA COVID-19 vaccine uptake in pregnancy: A large-scale registry-based linkage study

Jovan Elyass [a,b], Anteneh Desalegn [a], Nhung T.H. Trinh [a], Saima Orangzeb [a], Mahmoud Zidan [a], Hedvig Nordeng [a,c], Angela Lupattelli [a,*]

[a] PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway
[b] Université Bordeaux, INSERM, Bordeaux Population Health, Bordeaux, France
[c] Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

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ABSTRACT

The association between maternal COVID-19 vaccination in pregnancy and factors such as high risk for severe COVID-19, pre-existing asthma, prior adverse reproductive history, or paternal COVID-19 vaccination during pregnancy, remains unclear. The aim of this study is two-fold: (i) to describe uptake of COVID-19 vaccine during pregnancy by maternal risk for severe COVID-19 and asthma, and (ii) to comprehensively examine individual and familial factors associated with vaccine uptake during pregnancy in Norway. Based on nation-wide registry-linkage data in Norway, we included 101,659 deliveries with gestational length ≥12 weeks, in 2021–2022. Our outcome measure was uptake of at least one dose of mRNA COVID-19 vaccine during pregnancy, using a narrow (first ever dose) and broad (any dose) definition. We fit univariate and multivariate modified Poisson regression models, clustered by county of residency and adjusted for calendar time, to estimate risk ratios (RR) with 95 % Confidence Intervals (CIs). Gestational uptake of any COVID-19 vaccine dose increased from <1 % before mid Aug-2021, to 38.8 % in the rest of 2021, and 48.9 % in 2022. Only 28.8 % and 33.9 % pregnant individuals with high risk for severe COVID-19 or asthma, respectively, received at least one COVID-19 vaccine dose. Paternal COVID-19 vaccination was strongly associated with greater vaccine uptake by pregnant individuals (adjusted RR: 7.2, 95 % CI: 6.8–7.5). Maternal SARS-CoV-2 infection pre-pregnancy (adjusted RR: 0.31, 95 % CI: 0.26, 0.37), familial and individual migrant status were associated with a considerable decreased likelihood of vaccine uptake in pregnancy. History of miscarriage or pregnancy with congenital anomaly were not associated with vaccine uptake. Despite rising COVID-19 vaccine rates in pregnancy, uptake remained low for high-risk individuals. Paternal vaccination, pre-pregnancy infection, migration status, and maternal citizenship were strongly associated with prenatal vaccine uptake. This knowledge can inform tailoring of future vaccination campaigns.

1. Introduction

Pregnant individuals have substantial higher risk of severe COVID-19 and death than non-pregnant counterparts, primarily if unvaccinated [1–4]. Prenatal SARS-CoV-2 infection also increases the risk of multiple adverse pregnancy and child outcomes [5–10]. With emerging reassuring data about the safety of mRNA COVID-19 vaccine in pregnancy [11], there is consensus that the benefit of prenatal vaccination outweighs any potential risk to both mother and child [12].

In Norway, adults of childbearing age working as healthcare professionals or having conditions associated with high risk of severe COVID-19 illness were prioritized for COVID-19 vaccination in the beginning of 2021 [13]. In May 2021, all people aged 18–24 or 40–44 years were offered the first COVID-19 vaccine dose, and individuals in the age band 25–39 years came next in the national vaccination roll-out [13]. In Norway, the vaccination coverage with at least one dose of the COVID-19 vaccine was high among people of fertile age (88–92 %) during 2021 [14,15].

When it comes to pregnant individuals, national health authorities and professional medical organizations worldwide started recommending mRNA COVID-19 vaccination in this population, approximately in the second half of 2021 [12,16–18]. In August 2021, the Norwegian

* Corresponding author at: University of Oslo, Faculty of Mathematics and Natural Sciences, Department of Pharmacy, 0316 Oslo, Norway.
E-mail address: angela.lupattelli@farmasi.uio.no (A. Lupattelli).

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authorities recommended mRNA COVID-19 vaccination during the second and third trimesters, while for the first trimester, the risk of severe illness in the woman or of high exposure to the virus had to be considered. By January 2022, vaccination was recommended at any trimester [19]. Although COVID-19 vaccination in pregnancy has increased following these recommendations, including in Norway [20], low uptake remains a challenge in individuals with lower education or younger age, living alone, and with migrant background [20–23]. In addition, the extent of vaccine uptake among pregnant individuals with underlying health risk for severe COVID-19, remains insufficiently studied [24].

Studying vaccine uptake in pregnancy only in relation to maternal sociodemographic and broadly defined migrant status, is insufficient for informing targeted vaccination campaigns and clinical counselling. Multiple studies have confirmed that lack of knowledge [25], unrealistic risk perceptions [26], and fear of adverse vaccine effects on the child are major drivers of COVID-19 vaccine hesitancy among pregnant individuals [27–29]. Yet, the role of adverse reproductive history and prior lived experience of poorer delivery outcomes is unclear. Because having a family member vaccinated against COVID-19 is related to lower vaccine hesitancy in pregnant individuals [24], understanding the specific contribution of paternal COVID-19 vaccination is critical.

The aim of this study is two-fold: (i) to describe the uptake of mRNA COVID-19 vaccine during pregnancy in Norway during a two-years' time span and according to maternal risk for severe COVID-19 and asthma; (ii) to examine the association of a broad set of individual and familial factors, including prior adverse pregnancy outcomes and paternal COVID-19 vaccination, with vaccine uptake during pregnancy. mRNA COVID-19 vaccine (hereafter, COVID-19 vaccine) uptake was examined as receipt of any dose (broad definition) and as first ever dose (narrow definition) during pregnancy.

2. Materials and methods

2.1. Data sources

This study is based on data from Medical Birth Registry of Norway (MBRN), the Norwegian Immunisation Registry (SYSVAK), the Norwegian Surveillance System for Communicable Diseases (MSIS), Statistics Norway (SSB), the Population Registry, the Norwegian Control and Payment of Health Reimbursements Database (KUHR), and the Norwegian Patient Registry (NPR). Linkage across these registries were facilitated using unique personal identification numbers.

The MBRN is a population-based registry containing information on all births in Norway since 1967 [30]. It is based on mandatory notification of all pregnancies lasting more than 12 weeks and contains various information on both mother and infant(s). The SYSVAK is a national electronic immunisation register based on mandatory records of individual vaccination since birth and includes the specific code and name of each vaccine, and date of vaccination [31]. The MSIS includes mandatory records of all polymerase chain reaction (PCR) SARS-CoV-2 tests and their results based on reports from municipal health officers and laboratories. SSB is a central agency that provides official statistics, including demographics, housing conditions, education and income [32]. The Population Registry collects information about residents in Norway and their citizenships. The KUHR provides comprehensive records of medical diagnoses given in primary and secondary outpatient care; the diagnosis classification follows the International Classification of Diseases, version 10 (ICD-10) and the International Classification of Primary Care (ICPC-2/ICPC-2B). The NPR contains information on specialist outpatient and inpatient care, and diagnostic codes follow the ICD-10 classification [33].

2.2. Study population

We included all singleton pregnancies with gestational length greater than 12 weeks as registered in the MBRN with delivery date between 1-Jan-2021 and 31-Dec-2022. We excluded records with missing maternal identification number or missing gestational age, and individuals who received a non-RNA COVID-19 vaccine (see Fig. S1). The latter exclusion criterion was applied since the mRNA based vaccines by Pfizer-BioNTech and Moderna were those administered in the national vaccine roll-out [13]. To achieve the final study population for examining first dose vaccine uptake during pregnancy, we further excluded individuals with uptake of at least one mRNA COVID-19 vaccine pre-pregnancy start (n = 12,951).

2.3. COVID-19 vaccine uptake

Vaccine uptake during pregnancy was defined as receipt of at least one dose (broad definition) and as first ever dose (narrow definition) of any mRNA COVID-19 vaccine, as recorded in the SYSVAK, between the estimated last menstrual period date (LMP) and date of delivery. The LMP date was calculated by subtracting gestational length in days, ascertained via ultrasound, from the date of delivery. We did not consider non-mRNA COVID-19 vaccines as these were not primarily used in the vaccination program in Norway.

2.4. Individual and familial factors

We examined three sets of individual and familial factors, as described in detail in Table S1: (i) sociodemographic and life-style characteristics; (ii) maternal health, vaccination, and reproductive history; (iii) familial migration status and paternal COVID-19 vaccination. Maternal sociodemographic and life-style factors included: age, parity, marital and employment status, body mass index (BMI) at pregnancy start, and smoking before pregnancy, as ascertained in the MBRN. The SSB provided information on maternal educational level. Maternal health, vaccination and reproductive history included pre-existing epilepsy, whether the pregnancy was secondary to in-vitro fertility treatment (as ascertained in the MBRN), human-papilloma virus (HPV) and influenza vaccination within the past 10 years, as well as influenza vaccination in prior pregnancy. We defined pregnant individuals as having "low", "moderate" or "high" risk for severe COVID-19 according to the Norwegian Institute of Public Health (NIPH) classification for vaccine prioritization [34]. The definition is based on diagnosis codes from the NPR and KUHR with a look-back period of five years before LMP (see Table S2). Asthma was not included in the risk grouping as done by the NIPH, but considered as separate factor, due to the inability of identifying uncontrolled asthma. The MBRN provided information on maternal history of pregnancy loss (miscarriage or stillbirth), prior foetus/child with any major congenital anomaly, prior caesarean section, or premature delivery in the past 10 years. Familial factors included paternal COVID-19 vaccination during the pregnancy window, parental migration status, and granular information about maternal primary citizenship (grouped into regions). We separately examined associations with SARS-CoV-2 infection, defined as at least one positive PCR test in the MSIS during the six months before LMP.

Up to 36.5 % of observations had missing data on at least one of the examined factors, mainly maternal occupation, education, and smoking status. Incomplete data on prior pregnancy outcomes and reproductive history, occupation, education, smoking status, paternal age, and migration status, were imputed using multiple imputation with chained equation (ten replications), assuming data were missing at random. The imputation model included vaccine, sociodemographic- and health-related variables [35,36].

2.5. Statistical analyses

We conducted descriptive statistics and then three sets of forward stepwise modified Poisson regression models, clustered by the individual's county of residency and adjusted by calendar time of delivery,

with COVID-19 vaccine uptake as binary outcome variable. We fit separate models for the narrow and broad definition of vaccine uptake during pregnancy [37,38]. In the former analysis, individuals with at least one dose of COVID-19 vaccine pre-pregnancy were excluded. We assessed separately (i) sociodemographic and life-style characteristics; (ii) maternal health, vaccination and reproductive history; and (iii) familial migration status and paternal COVID-19 vaccination, to avoid multicollinearity and to better distinguish the role of each variable set. Candidate variables were first selected based on a p-value of <0.20 in the univariable regression model. Selected variables were then included in a unique multivariable model, and variables with no role ($p > 0.05$) or yielding a change less than 20 % in the beta coefficients of the retained variables were removed [37]. The final multiple regression model included only statistically significant factors and those influencing substantially the effect estimate of the retained factors [37]. Associations with SARS-CoV-2 infection pre-pregnancy were examined separately, and the multivariable regression models were adjusted for maternal education and age. Results are presented as risk ratios (RR) with the corresponding 95 % Confidence Intervals (CI) for each factor examined. Data analyses was performed using STATA MP v.18.

In sub-analyses, we replicated the regression models separately in pregnancies with delivery date before and after the 18-Aug-2021, to appraise whether factors were consistently associated with any dose vaccine uptake before and after the favourable national recommendation of vaccination in pregnancy. The date 18-Aug-2021 marks major revisions in national recommendations favouring COVID-19 vaccination during 2nd and 3rd trimesters, as well as 1st trimester if the benefit outweighs the risks [18]. To better appraise the associations of prior pregnancy outcomes with vaccine uptake by parity, we replicated the regression model of "Maternal health, vaccination, and reproductive history" factors among multiparous pregnancies.

3. Results

The study population included 101,659 pregnant individuals with delivery date between 1-Jan-2021 through 31-Dec-2022 (Fig. S1), whereof 30.0 % (30,518/101,659) received at least one dose of the COVID-19 vaccine during pregnancy. Of the 30,518 individuals who received COVID-19 vaccine during pregnancy, 41.4 % (12,951/30,518) had received at least one dose pre-pregnancy (Table S3). Among those individuals with no COVID-19 vaccination pre-pregnancy, 19.8 % (17,567/88,708) had uptake of their first dose of the COVID-19 vaccine specifically during gestation. Most pregnant individuals had one (15,164/30,518: 49.7 %) or two (14,474/30,518: 47.4 %) cumulative doses taken specifically during gestation (Table S3).

Fig. S2 shows vaccine uptake by calendar time and date of delivery. Before 18-Aug-2021, vaccine uptake in pregnancy was 0.9 % and mainly in the third trimester (92.0 % of vaccinations). This proportion increased to 38.8 % in the rest of 2021 and to 48.9 % in 2022 (Table S4). In 2021, any dose vaccine uptake generally coincided with first dose uptake, but not in 2022 (Table S4). Overall, the gestational timing of any dose vaccine uptake was 32.1 % (n = 9,780) in the first trimester, 57.2 % (n = 17,442) in the second, and 35.9 % (n = 10,947) in the third trimester.

Table 1 shows the distribution of baseline individual and familial factors by any and first dose COVID-19 vaccine uptake during pregnancy. As shown in Table 2, only 28.8 % and 13.8 % of pregnant individuals with high risk for severe COVID-19 received respectively any dose or the first vaccine dose during gestation. Vaccine uptake was about 2–4 % higher in women with pre-existing asthma than in their counterpart.

Fig. 1 shows which factors among sociodemographic and life-style characteristics (Panels A-B), and maternal health, vaccination, and reproductive history (Panels C-D) were associated with any dose and first dose vaccine uptake during pregnancy. Fig. 2 shows associations with familial migration status and paternal COVID-19 vaccination. Results of the univariate analyses are shown in Tables S5 and S6. Lower

Table 1
Baseline characteristics by mRNA COVID-19 vaccine uptake during pregnancy, as any dose and first dose uptake. Numbers are presented as n with % unless otherwise specified.

	Vaccine uptake during pregnancy, any dose				Vaccine uptake during pregnancy, first dose*	
	No N = 71,141		Yes N = 30,518		Yes N = 17, 567	
Sociodemographic and life-style characteristics						
Maternal age in years; mean & SD	30.9	4.7	31.5	4.5	31.4	4.5
Nulliparous (yes)	29,721	41.8	13,609	44.6	7,668	43.7
Married/cohabiting (yes)	66,790	93.9	29,131	95.5	16,714	95.1
Missing	17	0.0	<5	–	<5	–
Occupation						
Active working/ employed	48,186	67.7	23,081	75.6	13,063	74.4
Not working	10,829	15.2	2,876	9.4	1,834	10.4
Missing	12,126	17.0	4,561	14.9	2,670	15.2
Education						
High school	14,561	20.5	5,410	17.7	3,237	18.4
Higher than high school	38,387	54.0	20,668	67.7	11,470	65.3
Lower than high school	11,232	15.8	3,098	10.2	1,971	11.2
Missing	6,961	9.8	1,342	4.4	889	5.1
Preconception BMI; mean & SD	25.9	5.1	25.1	5.1	25.0	5.1
Smoking pre-pregnancy (yes)	3,477	4.9	1,070	3.5	687	3.9
Missing	9,320	13.1	3,620	11.9	1,850	10.5
Maternal health, other vaccinations, and reproductive history						
Preexisting epilepsy (yes)	435	0.6	193	0.6	113	0.6
Pregnancy secondary to IVF (yes)	2,810	3.9	1,453	4.8	840	4.8
HPV vaccine within 10 years pre-pregnancy (yes)	19,456	27.3	10,137	33.2	5,542	31.5
Influenza vaccine within 10 years pre-pregnancy (yes)	18,509	26.0	11,029	36.1	5,423	30.9
Influenza vaccine in prior pregnancy (yes)	6,710	9.4	4,320	14.2	2,254	12.8
Risk for severe COVID-19						
Low	70,421	99.0	30,192	98.9	17,410	99.1
Moderate	532	0.7	250	0.8	127	0.7
High	188	0.3	76	0.2	30	0.2
Pre-existing asthma (yes)	4,560	6.4	2,338	7.7	1,272	7.2
History of miscarriage or stillbirth (yes)	17,361	24.4	7,328	24.0	4,385	25.0
Missing	762	1.1	138	0.5	64	0.4
Prior cesarean section (yes)	7,153	10.1	2,771	9.1	1,625	9.3
Prior pregnancy with major congenital anomaly (yes)	437	0.6	196	0.6	113	0.6
Missing	3,834	5.4	1,012	3.3	660	3.8
Prior premature delivery (yes)	1,682	2.4	678	2.2	382	2.2
Missing	3,915	5.5	1,037	3.4	674	3.8
Positive Sars-CoV-2 6 months pre-pregnancy (yes)	1,810	2.5	351	1.2	192	1.1
Familial migration status and paternal COVID-19 vaccination						
Maternal primary country of citizenship						
Norway	52,618	74.0	26,146	85.7	14,888	84.7
Scandinavia	1,526	2.1	742	2.4	445	2.5
West/South Europe	1,158	1.6	560	1.8	310	1.8

(continued on next page)

Table 1 (*continued*)

	Vaccine uptake during pregnancy, any dose				Vaccine uptake during pregnancy, first dose*	
	No N = 71,141		Yes N = 30,518		Yes N = 17, 567	
Eastern Europe	6,912	9.7	979	3.2	608	3.5
Middle East	1,226	1.7	183	0.6	87	0.5
North America and Oceania	297	0.4	155	0.5	94	0.5
South and Central America	362	0.5	154	0.5	316	1.8
Africa	3,264	4.6	477	1.6	55	0.3
East and North-East Asia	230	0.3	96	0.3	55	0.3
North-Central Asia	537	0.8	82	0.3	285	1.6
South-East Asia	1,159	1.6	448	1.5	305	1.7
South and South-West Asia	1,852	2.6	496	1.6	119	0.7
Maternal migration status						
Born in Norway, both parents from Norway	43,709	61.4	22,985	75.3	13,058	74.3
Born in Norway or abroad, at least one parent from Norway	3,785	5.3	1,972	6.5	1,129	6.4
Migrated to Norway	21,906	30.8	5,108	16.7	3,139	17.9
Born in Norway from migrant parents	1,739	2.4	453	1.5	241	1.4
Missing	<5	–	–	–	–	–
Paternal migration status						
Born in Norway, both parents from Norway	43,679	61.4	22,927	75.1	13,047	74.3
Born in Norway or abroad, at least one parent from Norway	3,538	5.0	1,828	6.0	1,054	6.0
Migrated to Norway	20,082	28.2	4,706	15.4	2,883	16.4
Born in Norway from migrant parents	1,457	2.0	439	1.4	238	1.4
Missing	2,385	3.4	618	2.0	345	2.0
Paternal COVID-19 vaccination during pregnancy (yes)	22,421	31.5	27,124	88.9	16,612	94.6
Paternal age; mean & SD	33.5	5.5	33.7	5.6	33.7	5.7

Abbreviations: SD = Standard deviation; IVF = in-vitro fertility treatment.

education and not working/unemployed status were consistently associated with a decreased likelihood of vaccine uptake in pregnancy, both as any and first dose. Maternal health risk for severe COVID-19, history of prior pregnancies with congenital anomaly or miscarriages were not associated with any dose vaccine uptake in pregnancy. Only history of caesarean section and premature delivery was consistently associated with a negligible lower likelihood of vaccine uptake, using both definitions. Paternal COVID-19 vaccination during the pregnancy window was strongly associated with greater vaccine uptake in pregnancy, and the magnitude of this association was larger for first dose uptake. As shown in Fig. 2, different familial migration and main citizenship statuses were strongly associated with vaccine uptake in pregnancy, using both definitions. Maternal SARS-CoV-2 infection in the six months pre-pregnancy was consistently associated with a substantial lower likelihood of uptake of any dose (RR: 0.31, 95 % CI: 0.26, 0.37) or first dose (RR: 0.32, 95 % CI: 0.26, 0.41).

Factors such as smoking before pregnancy, IVF, and uptake of other non-COVID-19 vaccines were not consistently associated with any vaccine dose uptake in terms of direction of the association and/or effect size, before and after the positive national recommendations towards COVID-19 vaccination in pregnancy (Table S7). Fig. S3 shows associations between maternal health, vaccination, and reproductive history factors and vaccine uptake, as ever and first dose, among multiparous pregnancies.

4. Discussion

This study reports increasing rates of COVID-19 any dose vaccine uptake in pregnancy, spanning from less than 1 % among deliveries before mid Aug-2021, to 38.8 % in the rest of 2021, and to 48.9 % in 2022. During the overall period, only three out of ten individuals with high risk for severe COVID-19 received at least one COVID-19 vaccine dose while being pregnant, and this estimate decreased to 14 % for first dose uptake. Being at high-risk for severe COVID-19 did not correlate with greater vaccine uptake in pregnancy, but maternal pre-existing asthma did so (9–10 % higher likelihood). We found no evidence that prior miscarriage or pregnancy with congenital anomaly were related to lower vaccine uptake. Only history of caesarean section and premature delivery were negatively associated with COVID-19 vaccine uptake, albeit the effect size of these associations was negligible, especially among multiparous individuals. Paternal COVID-19 vaccination during the pregnancy window emerged as major factor associated with vaccine uptake in pregnancy, and the magnitude of this association was exceptionally large for first dose uptake. Individual maternal factors such as smoking, being unemployed, multiparity, lower education, and younger age were only moderately associated with lower COVID-19 vaccine uptake during pregnancy, whilst the association magnitude was substantial for SARS-CoV-2 infection in the six months pre-pregnancy (68–69 % reduced likelihood). Familial and individual migrant status, and maternal main citizenship from the Middle East, Africa, Eastern Europe, or North-Central Asia, were associated with a considerable decreased likelihood of vaccine uptake while being pregnant.

This study extends prior literature by identifying multiple factors at individual and familial level associated with COVID-19 vaccine uptake during pregnancy and reports novel uptake rates by maternal underlying risk for severe COVID-19 during a two-years period. Our over time

Table 2
Uptake of mRNA COVID-19 vaccine during pregnancy by maternal risk for severe COVID-19 or pre-existing asthma.

	Risk for severe COVID-19					
	Low		Moderate		High	
	n	*(95 CI)*	*n*	*(95 CI)*	*n*	*(95 CI)*
Any dose vaccine uptake during pregnancy (yes)	30,192	30.0 (29.7–30.3)	250	32.0 (28.8–35.3)	76	28.8 (23.6–34.5)
First dose vaccine uptake during pregnancy (yes)	17,410	19.8 (20.0–20.1)	127	19.3 (16.4–22.5)	30	13.8 (9.9–19.0)
	Pre-existing asthma					
	No		Yes			
	n	*(95 CI)*	*n*	*(95 CI)*		
Any dose vaccine uptake during pregnancy (yes)	28,180	29.7 (29.4–30.0)	2,338	33.9 (32.8–35.0)		
First dose vaccine uptake during pregnancy (yes)*	16,295	19.7 (19.4–19.9)	1,272	21.8 (20.8–22.9)		

Abbreviations: CI = Confidence Interval.

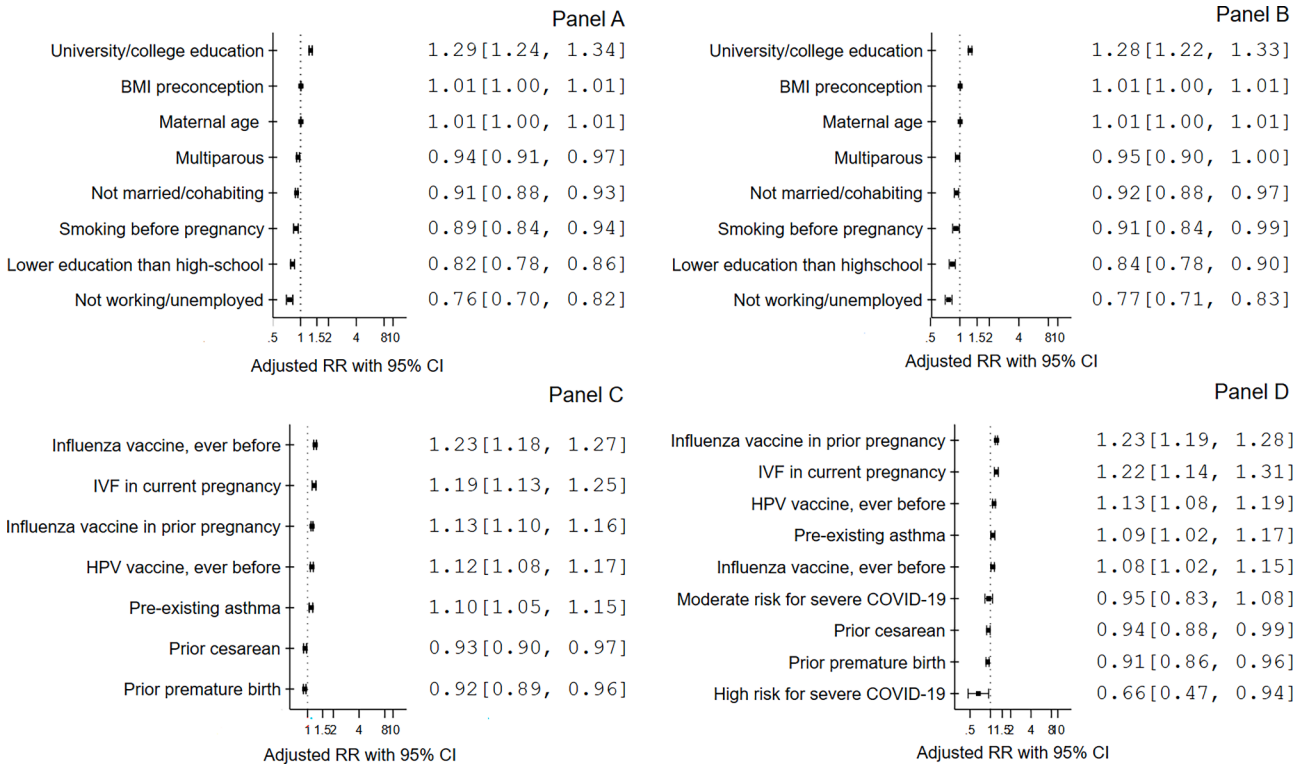

Fig. 1. Associations of sociodemographic and life-style characteristics (Panel A for any dose, Panel B first dose), maternal health, vaccination, and reproductive history (Panel C for any dose, Panel D for first dose) with COVID-19 vaccine uptake in pregnancy. Abbreviations: RR = Risk Ratio; CI = Confidence Interval. All multivariable models are adjusted by calendar time of childbirth, and for clustering by maternal region of residency. The reference categories in Panels A-B include: "high-school education" for educational level, and the counterparts of the other factors (e.g., "married/cohabiting" is reference group for "not married/cohabiting"). In Panels C-D, the reference categories are "no" for all factors (e.g. "No prior premature birth"). Non_COVID-19 vaccinations ever before and history of adverse outcomes are measured within ten years before pregnancy start.

increasing rates of COVID-19 vaccine uptake by pregnant individuals align with prior research including data from Norway up to May 2022, and reflect trust in the national vaccine recommendations [20,39,40]. Any dose COVID-19 vaccine uptake largely coincided with first dose uptake by pregnant individuals in the period between 18-Aug-2021 and end of 2021, which is encouraging. The new emerging knowledge about the favourable reproductive safety of prenatal COVID-19 vaccine exposure may have favoured greater acceptance of COVID-19 vaccination in pregnancy over time [11,41].

The observed low rate of vaccine uptake among pregnant individuals with high risk for severe COVID-19 was consistent for any and first dose vaccine uptake, which is somewhat worrisome. Pregnant individuals with high-risk also had lower likelihood of first dose vaccine uptake than their peers with no/low risk, which is an unexpected result. It is possible that the applied definition for severe COVID-19 risk group [34] may not be fully applicable to childbearing aged individuals as most of high-risk disorders, e.g. organ transplantation and cancer, are rare in this population. Prior research in Norway and Sweden [20] found individuals with pre-pregnancy comorbidities, as broad unique classification, to be more likely to get vaccinated during pregnancy than their peers, albeit the effect size was negligible (8–12 % higher likelihood). The disorders included in our high-risk classification do not fully coincide with those applied by Örtqvist et al. [20], which may explain the discrepant results. Furthermore, we considered pre-existing asthma as a stand-alone disorder, and this disorder was associated with greater vaccine uptake. Prioritizing high-risk individuals for vaccination is crucial due to their increased susceptibility to severe illness, and this also applies to pregnant individuals. In possible future pandemics, vaccination campaigns should better emphasize which specific high-risk disorders are critical for the pregnant and childbearing aged populations.

The substantial association between greater vaccine uptake in pregnancy and paternal COVID-19 vaccination during the pregnancy window deserves attention. A prior study [24] showed that pregnant individuals who had friend or family member vaccinated against COVID-19 had 84 % reduced odds of reporting vaccine hesitance than their counterparts, and partner support is critical in the context of pharmacotherapy in pregnancy [27,42]. Paternal migration status was an additional familial factor associated with lower vaccine uptake. Taken together, these data highlight the importance of vaccine educational campaigns for couples, and call for an active involvement of fathers at the phase of clinical counselling, to facilitate the decision-making process regarding benefits and risks of prenatal vaccination.

Although maternal unrealistic risk perceptions of vaccine exposure and fears of adverse effects on the child [26–29,43] were identified as key factors associated with vaccination hesitancy, we found no evidence that prior lived experience of miscarriage or pregnancy with congenital anomaly led to lower vaccine uptake. This result could be attributable to trust towards national authorities and to the provided emerging knowledge about the safety of COVID-19 vaccination for maternal-child health. Only history of prior caesarean section or premature delivery were linked to lower COVID-19 vaccine uptake in our analyses, albeit the effect size was negligible, especially in the analysis restricted to multiparous women. It is possible that vaccine recommendations by policy makers and national authorities did not specifically address possible risk of vaccination in relation to these two outcomes, as they are more subtle than miscarriage or congenital anomaly [44]. Overall, these data suggest that maternal adverse pregnancy history is not strongly related to negative perceptions and attitudes towards vaccination in pregnancy, at least in Norway [43]. Efforts should be made to investigate whether this result also applies to other national and societal context, because this is critical knowledge for providing tailored vaccination counselling to couples who are most hesitant.

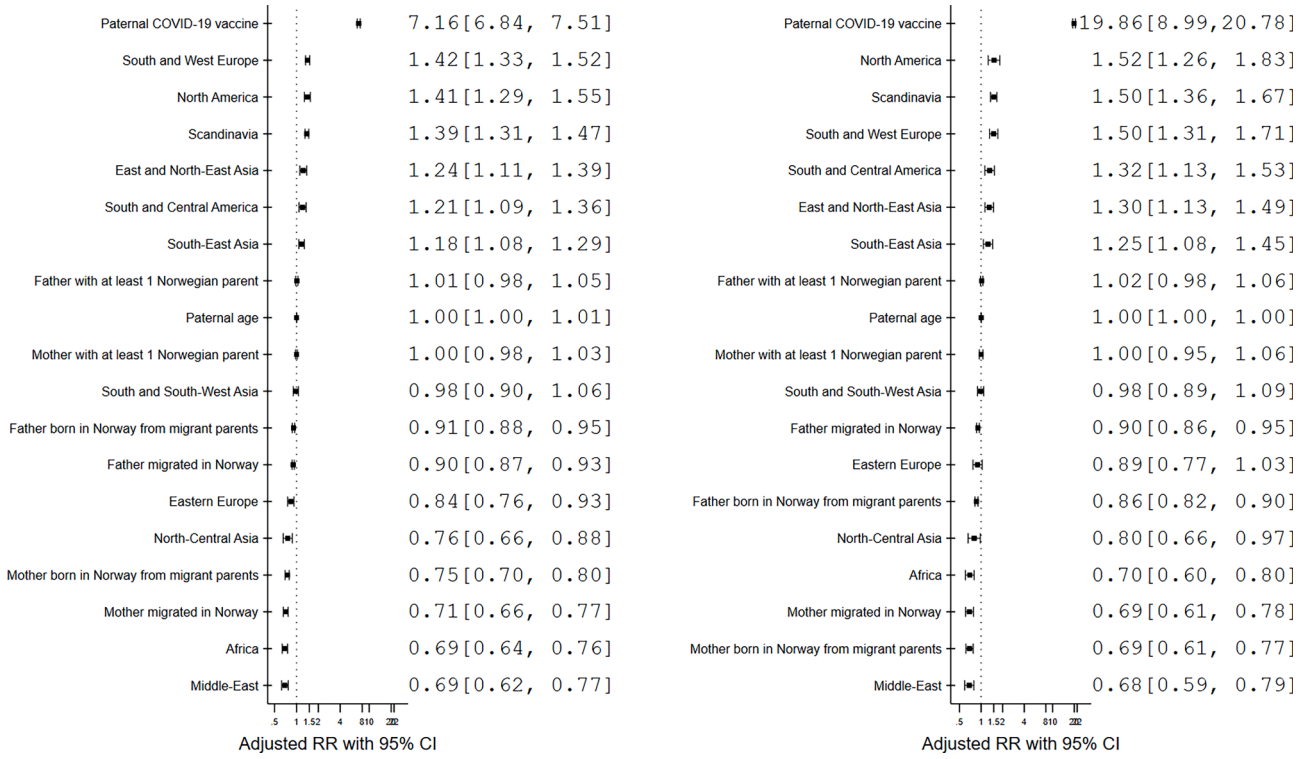

Fig. 2. Associations of familial migration status and paternal COVID-19 vaccination with vaccine uptake during pregnancy as any dose (Panel A) and first dose (Panel B) Abbreviations: RR = Risk Ratio; CI = Confidence Interval. The multivariable model is adjusted by calendar time of childbirth, and for clustering by maternal region of residency. The reference categories are "Norwegian primary citizenship", "Born in Norway from two Norwegian parents", and "No Paternal COVID-19 vaccine". Paternal COVID-19 vaccine was measured during the pregnancy window.

This study supports prior established associations between lower COVID-19 vaccine uptake in pregnancy among individuals being smokers, having lower education and income, younger age, multiparity, migrant status, and specific citizenships/ethnicities [20,24,45,46]. Our granular findings by maternal main citizenship support the need of vaccination campaigns tailored specifically to pregnant individuals from African countries, the Middle East, Eastern Europe, or North-central Asia. In line with prior data [24,46], this study shows that uptake of other vaccines, e.g. against influenza, is proxy of general positive attitude and trust towards vaccination, and this is linked to greater COVID-19 vaccine uptake rates even by pregnant individuals. Unlike other studies but also in line with other investigations [27,47], SARS-CoV-2 infection in the six months pre-pregnancy appeared to be a major factor associated with lower vaccine uptake by pregnant individuals in Norway. This may be explained by uncertainties regarding durability of natural immunity [48] coupled to maternal safety concerns about prenatal exposure to the COVID-19 vaccine [27].

5. Strengths and limitations

The study is based on multiple, nation-wide health registry data in Norway linked to the MBRN, which covers all deliveries since gestational week 12. The mandatory registration of COVID-19 vaccination in the SYSVAK minimizes risk of misclassification of vaccine uptake; since the SYSVAK records all vaccine doses received independently of pregnancy, the study could differentiate between any dose and first vaccine uptake in pregnant individuals. The comprehensive availability of clinical diagnoses from primary and secondary healthcare, coupled to obstetric records from the MBRN, enabled us to adequately classify maternal risk groups for severe COVID-19 and asthma. Information on prospective fathers, and the availability of ten years historical data for mothers, allowed us to explore a vast array of familial and individual factors associated with vaccine uptake in pregnancy, including granular details on maternal main citizenship. Lastly, we used multiple imputation to minimize risk of bias due to missing data [49].

This study also has some limitations that need consideration when interpreting the results. We used receipt of a vaccine dose as proxy of vaccine acceptance, which may not fully measure attitude/beliefs toward vaccination. The study could not explore the role of emotional, social, and religious factors as these are not measured in our national registries, although these may be important determinants of vaccine uptake [27]. Political and logistical aspects related to the distribution of the COVID-19 vaccine in the various counties in Norway was not measured in the study; to address changes of vaccination recommendation, we repeated the association and descriptive analyses for the period before and after 18-Aug-2021 [34]. Vaccine doses given abroad need manual retrospective registration in SYSVAK, leading to uncertainty about how many pregnant individuals received vaccines overseas without official records in Norway. However, this risk is considered as minimal, given the necessity of vaccine registration during the study period. The MBRN does not provide granular information about the type of occupation in pregnant individuals, and thereby we could not examine the role of healthcare worker status on vaccine uptake in pregnancy. Although we examined separately three sets of individual and familial factors and their standard errors in the final multivariate models were assessed as satisfactory, we cannot rule out the risk for multicollinearity or for interaction effects.

6. Conclusion

In this registry-linkage study, we observed over time increasing rates of COVID-19 vaccine uptake during pregnancy, and any dose uptake largely coincided with first dose uptake in the period between 18-Aug-2021 through end of 2021. However, COVID-19 vaccination remained low among pregnant individuals with high risk for severe COVID-19. Paternal COVID-19 vaccination during the pregnancy window, SARS-

CoV-2 infection pre-pregnancy, individual and familial migration status, and specific maternal main citizenships, emerged as important factors associated with COVID-19 vaccine uptake during pregnancy. We found no evidence that prior miscarriage or pregnancy with congenital anomaly were related to lower vaccine uptake. These findings are useful for the design of targeted intervention and educational vaccination campaigns for couples in possible future pandemics, to facilitate an informed, evidence-based vaccine uptake by pregnant populations.

Ethics approval

The Regional Committee for Medical and Health Ethics of South/East Norway (no. 285687) approved the study. The Norwegian Data Protection Services for research and the University of Oslo approved the Data Protection Impact Assessment – DPIA (no. 341884).

CRediT authorship contribution statement

Jovan Elyass: Writing – original draft, Formal analysis, Data curation. **Anteneh Desalegn: . Nhung T.H. Trinh:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Saima Orangzeb:** Writing – review & editing, Validation, Data curation. **Mahmoud Zidan:** Writing – review & editing, Validation, Data curation. **Hedvig Nordeng:** Writing – review & editing, Validation, Methodology. **Angela Lupattelli:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Angela Lupattelli reports financial support was provided by European Union. This work is part of the VERDI project (101045989) which is funded by the European Union. Views and opinions expressed are, however, those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All relevant data are within the paper and its Supporting Information files. No additional data are available.

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Contributions of authors

AL, AD and NTHT conceived the study. AL applied for the study data. AL and JE performed the data analysis, and AD contributed to data curation. AL and JE wrote the initial draft. JE, AD, NTHT, SO, MZ, HN, and AL contributed to data interpretation and to writing the final manuscript. AL obtained funding. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126171.

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