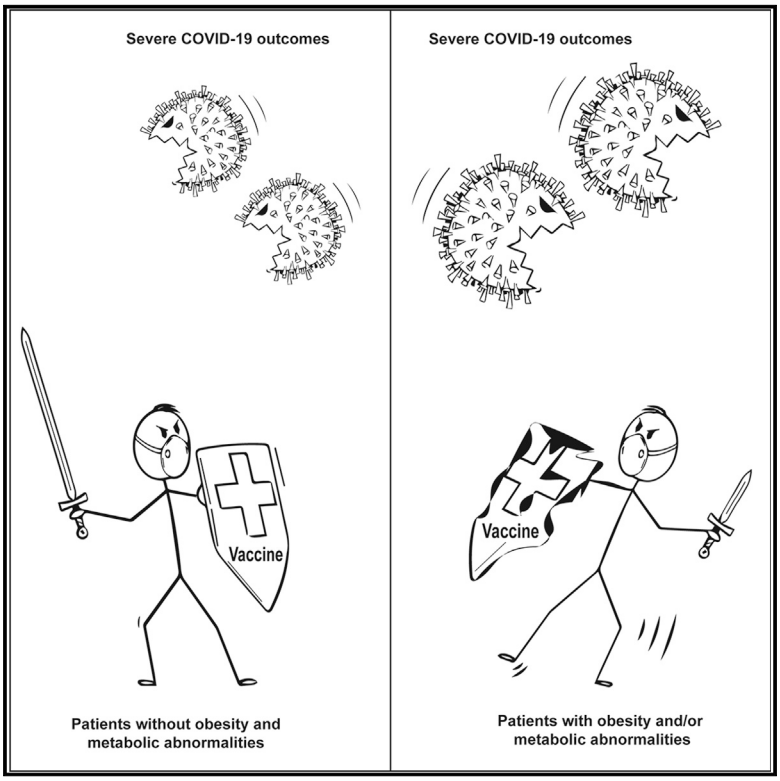
Cell Metabolism
Clinical and Translational Report

The effects of obesity and metabolic abnormalities on severe COVID-19-related outcomes after vaccination: A population-based study

Graphical abstract



Highlights

- Obesity and metabolic abnormalities are highly prevalent in patients with severe COVID-19
- Obesity and metabolic abnormalities are associated with an increased risk of severe COVID-19
- In vaccinated patients, metabolic abnormalities are risk factors for severe COVID-19
- Interventions targeting metabolic abnormalities may reduce the risk of severe COVID-19

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In brief

Fan et al. show that obesity and metabolic abnormalities were modifiable risk factors for severe COVID-19 events in vaccinated patients. When metabolic abnormalities (namely, hyperglycemia, hyperlipidemia, or hypertension) were present, regardless of obesity, the risk of severe COVID-19 was higher than that of metabolically normal people. Moreover, pharmacological interventions targeting such abnormalities were significantly associated with a reduced risk for this outcome.

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The effects of obesity and metabolic abnormalities on severe COVID-19-related outcomes after vaccination: A population-based study

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SUMMARY

Breakthrough SARS-CoV-2 infections of vaccinated individuals are being reported globally, resulting in an increased risk of hospitalization and death among such patients. Therefore, it is crucial to identify the modifiable risk factors that may affect the protective efficacy of vaccine use against the development of severe COVID-19 and thus to initiate early medical interventions. Here, in population-based studies using the UK Biobank database and the 2021 National Health Interview Survey (NHIS), we analyzed 20,362 participants aged 50 years or older and 2,588 aged 18 years or older from both databases who tested positive for SARS-COV-2, of whom 33.1% and 67.7% received one or more doses of vaccine, respectively. In the UK Biobank, participants are followed from the vaccination date until October 18, 2021. We found that obesity and metabolic abnormalities (namely, hyperglycemia, hyperlipidemia, and hypertension) were modifiable factors for severe COVID-19 in vaccinated patients (all $p < 0.05$). When metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19 was higher than that of metabolically normal individuals (all $p < 0.05$). Moreover, pharmacological interventions targeting such abnormalities (namely, antihypertensive [adjusted hazard ratio (aHR) 0.64, 95% CI 0.48–0.86; $p = 0.003$], glucose-lowering [aHR 0.55, 95% CI 0.36–0.83; $p = 0.004$], and lipid-lowering treatments [aHR 0.50, 95% CI 0.37–0.68; $p < 0.001$]) were significantly associated with a reduced risk for this outcome. These results show that more proactive health management of patients with obesity and metabolic abnormalities is critical to reduce the incidence of severe COVID-19 after vaccination.

INTRODUCTION

The risk of SARS-CoV-2 infection, hospitalization, and death from COVID-19 has been strikingly reduced due to the implementation of COVID-19 vaccinations.[1,2] However, as vaccine effectiveness is less than 100%, breakthrough SARS-CoV-2 infections (defined as SARS-CoV-2 infections occurring in individuals despite their prior full vaccination) have been widely reported worldwide, resulting in increased hospitalization and death even among vaccinated patients.[3–5] Therefore, it is crucial to identify those at higher risk of developing severe COVID-19 despite previous full vaccination and to initiate an early medical intervention among such individuals.

Prior to the introduction of COVID-19 vaccines, obesity and metabolic abnormalities (characterized by hypertension, hyperlipidemia, and hyperglycemia) were found to be independently

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Table 1. Demographic and clinical characteristics of vaccinated and unvaccinated patients with severe COVID-19-related events

	Vaccinated			Non-vaccinated		
Group	No severe outcome (N = 6,461)	Severe outcome (N = 288)	p value	No severe outcome (N = 12,176)	Severe outcome (N = 1,437)	p value
Age (years)			<0.001			<0.001
<65	2,833 (43.8%)	41 (14.2%)		6,222 (51.1%)	373 (26.0%)	
≥65	3,628 (56.2%)	247 (85.8%)		5,954 (48.9%)	1,064 (74.0%)	
Gender			<0.001			<0.001
Female	3,471 (53.7%)	120 (41.7%)		6,653 (54.6%)	637 (44.3%)	
Male	2,990 (46.3%)	168 (58.3%)		5,523 (45.4%)	800 (55.7%)	
Race			0.499			<0.001
Non-white	345 (5.4%)	18 (6.3%)		1,197 (9.9%)	180 (12.6%)	
White	6,102 (94.6%)	269 (93.7%)		10,937 (90.1%)	1,248 (87.4%)	
Smoking status			<0.001			<0.001
Never	3,567 (55.3%)	124 (43.0%)		6,805 (56.2%)	654 (46.0%)	
Previous	2,266 (35.1%)	119 (41.3%)		4,054 (33.5%)	573 (40.3%)	
Current	617 (9.6%)	45 (15.6%)		1,259 (10.4%)	195 (13.7%)	
Alcohol abuse/dependence			<0.001			<0.001
No	6,343 (98.2%)	273 (94.8%)		11,999 (98.5%)	1,360 (94.6%)	
Yes	118 (1.8%)	15 (5.2%)		188 (1.5%)	77 (5.4%)	
Vaccine type			<0.001			
BNT162b2	1,985 (30.7%)	120 (41.7%)		–	–	–
ChAdOx1	4,476 (69.3%)	168 (58.3%)		–	–	–
Vaccination			<0.001			
Only one dose	558 (8.6%)	78 (27.1%)		–	–	–
Two or more dose	5,903 (91.4%)	210 (72.9%)		–	–	–
Obesity and metabolic disorders, N (%)						
Obesity			<0.001			<0.001
No	4,693 (72.6%)	173 (60.1%)		8,701 (71.5%)	728 (50.7%)	
Yes	1,768 (27.4%)	115 (39.9%)		3,475 (28.5%)	709 (49.3%)	
Hyperglycemia			<0.001			<0.001
No	5,907 (91.4%)	225 (78.1%)		10,978 (90.1%)	1,067 (74.3%)	
Yes	554 (8.6%)	63 (21.9%)		1,198 (9.8%)	370 (25.7%)	
Prediabetes			0.003			<0.001
No	6,275 (97.1%)	271 (94.1%)		11,810 (97.0%)	1,326 (92.3%)	
Yes	186 (2.9%)	17 (5.9%)		366 (3.0%)	111 (7.7%)	
Total diabetes mellitus			<0.001			<0.001
No	6,092 (94.3%)	242 (84.0%)		11,344 (93.2%)	1,178 (82.0%)	
Yes	369 (5.7%)	46 (16.0%)		832 (6.8%)	259 (18.0%)	
T1DM			<0.001			<0.001
No	6,431 (99.5%)	278 (96.5%)		12,125 (99.6%)	1,400 (97.4%)	
Yes	30 (0.5%)	10 (3.5%)		51 (0.4%)	37 (2.6%)	
T2DM			0.003			<0.001
No	6,122 (94.8%)	252 (87.5%)		11,395 (93.6%)	1215 (84.6%)	
Yes	339 (5.2%)	36 (12.5%)		781 (6.4%)	222 (15.4%)	
Hyperlipidemia			<0.001			<0.001
No	5,111 (79.1%)	156 (54.2%)		9,755 (80.1%)	793 (55.2%)	
Yes	1,350 (20.9%)	132 (45.8%)		2,421 (19.9%)	644 (44.8%)	
Hypertension			<0.001			<0.001
No	4,464 (69.1%)	139 (48.3%)		8,458 (69.5%)	675 (47.0%)	
Yes	1,997 (30.9%)	149 (51.7%)		3,718 (30.5%)	762 (53.0%)	

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Table 1. *Continued*

Group	Vaccinated			Non-vaccinated		
	No severe outcome (N = 6,461)	Severe outcome (N = 288)	p value	No severe outcome (N = 12,176)	Severe outcome (N = 1,437)	p value
Comorbidities, N (%)						
Asthma			0.038			<0.001
No	5,514 (85.3%)	233 (80.9%)		10,414 (85.5%)	1,130 (78.6%)	
Yes	947 (14.7%)	55 (19.1%)		1,762 (14.5%)	307 (21.4%)	
COPD			<0.001			<0.001
No	6,318 (97.8%)	253 (87.8%)		11,976 (98.4%)	1,322 (92.0%)	
Yes	143 (2.2%)	35 (12.2%)		200 (1.6%)	115 (8.1%)	
Chronic bronchitis			<0.001			<0.001
No	6,384 (98.8%)	277 (96.2%)		12,015 (98.7%)	1,392 (96.9%)	
Yes	77 (1.2%)	11 (3.8%)		161 (1.3%)	45 (3.1%)	
Interstitial lung disease			<0.001			<0.001
No	6,446 (99.8%)	280 (97.2%)		12,159 (99.9)	1,428 (99.4)	
Yes	15 (0.2%)	8 (2.8%)		17 (0.1%)	9 (0.6)	
Ischemic heart diseases			<0.001			<0.001
No	5,961 (92.3%)	228 (79.2%)		11,251 (92.4%)	1,165 (81.1%)	
Yes	500 (7.7%)	60 (20.8%)		925 (7.6%)	272 (18.9%)	
Heart failure			<0.001			<0.001
No	6,432 (99.6%)	279 (96.9%)		12,118 (99.5%)	1,386 (96.5%)	
Yes	29 (0.4%)	9 (3.1%)		58 (0.5%)	51 (3.5%)	
Liver cirrhosis			<0.001			<0.001
No	6,432 (99.6%)	280 (97.2%)		12,084 (99.2%)	1,386 (96.5%)	
Yes	29 (0.4%)	8 (2.8%)		92 (0.8) %	51 (3.5%)	
CKD			<0.001			<0.001
No	6,398 (99.0%)	274 (95.1%)		12,077 (99.2%)	1,374 (95.6%)	
Yes	63 (1.0%)	14 (4.9%)		99 (0.8%)	63 (4.4%)	
Dementia			0.047			<0.001
No	6,450 (99.8%)	286 (99.3%)		12,157 (99.8)	1,417 (98.6%)	
Yes	11 (0.2%)	2 (0.7%)		19 (0.2)	20 (1.4%)	
Mania, bipolar disorder, and depression			0.004			<0.001
No	5,939 (91.9%)	251 (87.2%)		11,209 (92.1%)	1,245 (86.6%)	
Yes	522 (8.1%)	37 (12.8%)		967 (7.9)	192 (13.4%)	
Sleep disorder			<0.001			<0.001
No	5,876 (90.9%)	243 (84.4%)		11,105 (91.2%)	1,216 (84.6%)	
Yes	585 (9.1%)	45 (15.6%)		1,071 (8.8%)	221 (15.4%)	
Osteoarthritis			<0.001			<0.001
No	5,878 (91.0%)	234 (81.2%)		11,147 (91.5%)	1,199 (83.4%)	
Yes	583 (9.0%)	54 (18.8%)		1,029 (8.5%)	238 (16.6%)	
Immunodeficiency			0.309			0.160
No	6,453 (99.9%)	287 (99.7%)		12,161 (99.9%)	1,437 (100%)	
Yes	8 (0.1%)	1 (0.3%)		15 (0.1%)	0 (0.0%)	
Clinical endpoints, N (%)						
COVID-19-related hospital admission			<0.001			<0.001
No	6,461 (100.0%)	11 (3.8%)		12,176 (100.0%)	86 (6.0%)	
Yes	0 (0.0%)	277 (96.2%)		0 (0.0%)	1,351 (94.0%)	
ICU hospital admission			<0.001			<0.001
No	6,461 (100.0%)	283 (98.3%)		12,176 (100%)	1,284 (89.4%)	

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Table 1. *Continued*

Group	Vaccinated			Non-vaccinated		
	No severe outcome (N = 6,461)	Severe outcome (N = 288)	p value	No severe outcome (N = 12,176)	Severe outcome (N = 1,437)	p value
Yes	0 (0.0%)	5 (1.7%)		0 (0.0%)	153 (10.6%)	
Death			<0.001			<0.001
Survival	6,461 (100%)	240 (83.3%)		12,176 (100%)	1,011 (70.4%)	
COVID-19-related deaths	0 (0.0%)	48 (16.7%)		0 (0.0%)	426 (29.6%)	

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney diseases; ICU, intensive care unit.

associated with an increased risk of severe COVID-19.[4,6,7] The global prevalence of obesity and metabolic abnormalities is quite high, with over 39% of adults being overweight and more than 600 million individuals with obesity.[8] It is estimated that globally 9.3% of the population has diabetes,[9] 26% has hypertension,[10] and 39% has elevated total cholesterol.[11] People with obesity often have a low degree of whole-body inflammation and a weakened immune response to infectious agents, and are thus more susceptible to infection,[4,6] which is also common in patients with diabetes, hypertension, or hyperlipidemia.[12] Previous studies have found that patients with obesity and/or diabetes demonstrate an impaired immune response to influenza A virus (IAV) vaccination and antimicrobial therapy.[4] The efficacy of COVID-19 vaccines might also be reduced in this population. However, prior studies have only assessed the association between diabetes or overweight/obesity and the risk of severe COVID-19 in previously vaccinated individuals.[13–15] Systematic assessments are lacking regarding the association between obesity and metabolic abnormalities and the risk of severe COVID-19 in non-vaccinated versus vaccinated patients and between vaccinated individuals with normal weight and no metabolic abnormalities and vaccinated individuals with overweight or obesity and metabolic abnormalities. Our study, by comparing such groups, is conducive for the identification of modifiable factors that, if targeted, could improve the ability of COVID-19 vaccines to protect patients from severe COVID-19.

It is now well established that the risk of breakthrough SARS-CoV-2 infections among the previously vaccinated, as well as the risk of severe COVID-19, is increased in patients with advanced age and chronic medical conditions.[13,14,16] However, an older age is an unchangeable risk factor, and patients with severe chronic diseases, such as coronary heart disease, liver cirrhosis, and chronic kidney disease, require clinical therapy due to their severe and rapidly progressing conditions,[17] even if they are not suffering from COVID-19. Solid evidence indicates that obesity, metabolic abnormalities, and multiple chronic diseases share important underlying pathomechanisms, including subclinical inflammation, insulin resistance, and immune dysfunction, which might explain their tight association with other medical conditions[12] and severe COVID-19. Moreover, studies have found that weight loss, along with antihypertensive, antidiabetic, and lipid-lowering therapies, play an important role in improving the outcomes of various chronic diseases, such as coronary heart disease,[18] chronic obstructive pulmonary disease (COPD),[19] chronic liver disease,[20] and chronic kidney disease,[21] suggesting that pharmacological interventions targeting metabolic abnormalities may be beneficial in reducing the risk of severe COVID-19-related events in individuals with such conditions and SARS-CoV-2 infection, which may improve the effectiveness of COVID-19 vaccines in protecting against severe COVID-19-related events.

To identify core modifiable risk factors for severe COVID-19 and effectively promote early intervention to minimize the risk of COVID-19-related hospitalizations and deaths in vaccinated patients, we conducted a prospective cohort study using data from the UK Biobank between December 8, 2020, and October 18, 2021, and a cross-sectional study based on data from the 2021 National Health Interview Survey (NHIS) to assess the association between risk factors, particularly obesity and metabolic abnormalities, and the risk of severe COVID-19 in vaccinated patients, as well as the role of pharmacological interventions targeting metabolic abnormalities in the risk of severe COVID-19.

RESULTS

Characteristics of the vaccinated and unvaccinated cohort in the UK Biobank study

Of 113,336 participants aged 50 years or older from the UK Biobank who had been tested for COVID-19, 54,319 (47.9%) received one or more doses of BNT162b2 or ChAdOx1 14 days or earlier before SARS-CoV-2 testing and 59,017 (52.1%) were unvaccinated or received their first dose within 14 days before testing. In this study, participants were considered vaccinated if they received one or more doses of vaccine 14 days or earlier before SARS-CoV-2 testing. Participants were considered as unvaccinated if they had never been vaccinated or received their first dose within 14 days before testing (Figures S1A and S1B). Vaccinated participants (6,749, 12.4%) had lower rates of COVID-19 infections than unvaccinated participants (13,613, 23.1%). Among those infected with SARS-CoV-2, the rates of hospitalization (4.1% versus 9.9%, $p < 0.001$) and death (0.7% versus 3.1%, $p < 0.001$) were lower in those who were vaccinated than among those who were not (Figure S1C). Of the vaccinated participants, 42,780 (78.8%) received two or more doses of vaccine; those considered fully vaccinated received two or more doses 14 days or earlier before SARS-CoV-2 testing. In addition, 21,757 (40.1%) received the BNT162b2 vaccine and 32,562 (59.9%) received the ChAdOx1 vaccine (Table 1). We recorded the distribution of SARS-CoV-2 infection, hospital admission, and deaths due to COVID-19 (vaccinated and unvaccinated participants) during the study period from December 8, 2020, to October 18, 2021 (Figure S2; Data S1), and they were consistent with the overall trend in the

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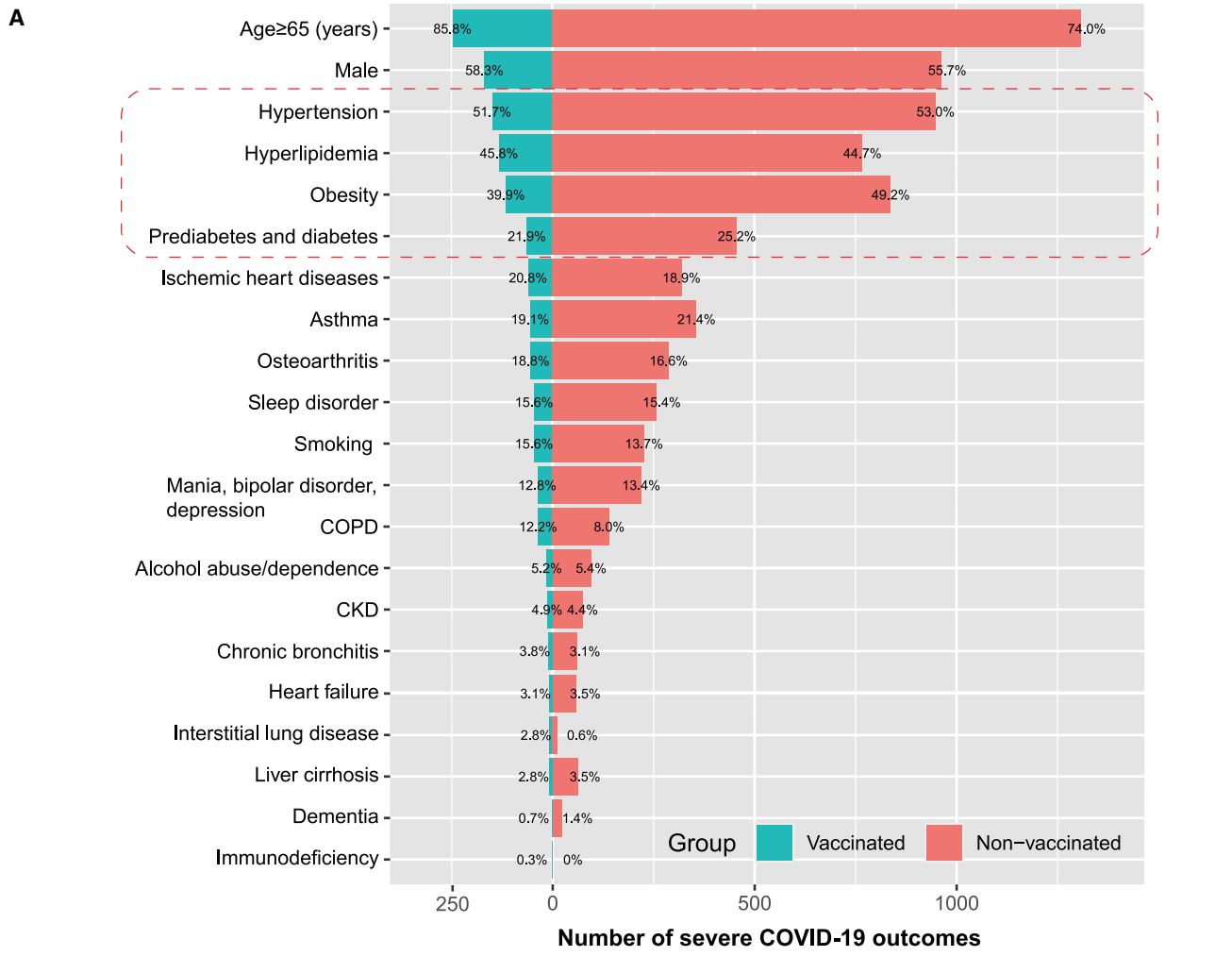

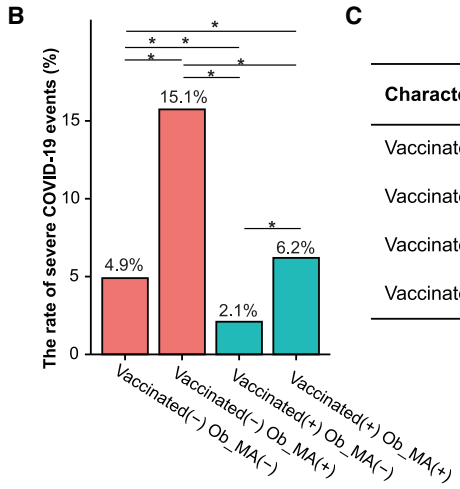

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Characteristics	N (%)	Severe COVID-19 outcomes (%)	HR (95% CI)	P value
Vaccinated(−) Ob_MA(−)	6175 (30.3)	302 (4.9)	1	<0.001
Vaccinated(−) Ob_MA(+)	7438 (36.5)	1124 (15.1)	2.32(2.03−2.65)	<0.001
Vaccinated(+) Ob_MA(−)	3228 (15.9)	69 (2.1)	0.41(0.32−0.54)	<0.001
Vaccinated(+) Ob_MA(+)	3521 (17.3)	219 (6.2)	0.93(0.77−1.11)	0.399

Figure 1. Demographic and clinical characteristics of vaccinated and unvaccinated patients with severe COVID-19-related events

(A) The number and proportion of multiple risk factors for severe COVID-19-related events in vaccinated and unvaccinated patients.

(B) The proportion of severe COVID-19-related events of different obesity and metabolic abnormalities and vaccination status, *p < 0.05.

(C) Association between status of obesity and metabolic abnormalities, vaccination, and severe COVID-19-related events.

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UK,[22] indicating that the UK Biobank is reliable and representative of the overall population.

Obesity and metabolic abnormalities and the severe COVID-19-related events in the UK Biobank study

In terms of demographic and clinical characteristics, similar to unvaccinated patients, 85.8% of participants who experienced a severe COVID-19-related clinical event 14 days or more after vaccination were elderly, 58.7% were male, 51.7% had hypertension, 45.5% had hyperlipidemia, 39.9% were obese, and 21.9% had prediabetes or diabetes (Figure 1A; Data S1). As shown in Figure 1B, when obesity or metabolic abnormalities were present, vaccinated patients had lower rates of severe COVID-19-related events compared with unvaccinated patients (15.1% versus 6.2%, $p < 0.05$), but these patients had higher rates of severe COVID-19-related events than vaccinated patients without obesity and metabolic abnormalities (6.2% versus 2.1%, $p < 0.05$). From Figure 1C, we found that in the absence of obesity and metabolic abnormalities, vaccinated individuals had a lower risk of severe COVID-19-related events compared with unvaccinated individuals (adjusted hazard ratio [aHR] 0.41, 95% CI 0.32–0.54; $p < 0.001$). However, there is no difference in the risk of severe COVID-19-related events between vaccinated patients with obesity or metabolic abnormalities and unvaccinated patients without obesity and metabolic abnormalities (aHR 0.93, 95% CI 0.77–1.11; $p = 0.34$).

Risk factors for severe COVID-19-related events among vaccinated participants in the UK Biobank study

We determined aHRs for the associations of demographic and clinical characteristics with severe COVID-19-related outcomes in vaccinated participants (Figure 2). Older, male, current smoking, alcohol abuse or dependence, obesity, diabetes, hyperlipidemia, hypertension, asthma, COPD, interstitial lung disease, ischemic heart disease, heart failure, liver cirrhosis, mania, bipolar disorder, depression, sleep disorders, and osteoarthritis increased the risk of severe COVID-19-related events in vaccinated participants (all $p < 0.05$). Patients fully vaccinated were protected against severe COVID-19 compared to a single dose (aHR 0.28, 95% CI 0.21–0.36; $p < 0.0001$). We also evaluated the aHRs for the correlation of risk factors with COVID-19-related hospitalizations and deaths. The association between the above exposure factors and the risk of COVID-19-related hospitalization (Table S1) or death (Table S2) was generally consistent with the above results. In addition, for fully vaccinated participants (Table S3) and unvaccinated participants (Table S4), the presence of the above risk factors also increased the risk of severe COVID-19-related events.

Metabolic moderators of the effects of multiple conditions on the risk of severe COVID-19 in the UK Biobank study

Notably, in addition to age and sex, patients with modifiable risk factors, such as obesity and metabolic abnormalities, had the highest proportion of severe COVID-19-related events (Figure 1A; Data S1). We found that over 75% of vaccinated (Figure 3A; Data S1) and unvaccinated patients (Figure S3A; Data S1) with severe COVID-19-related events had metabolic abnormalities and about 40% had both obesity and metabolic abnormalities in the presence of various risk factors. Here, we quantified how much the effects of common risk factors on severe COVID-19 are moderated through obesity and/or metabolic abnormalities. In both vaccinated and unvaccinated patients, we found that the presence of obesity and/or metabolic abnormalities enhanced the impact of multiple chronic conditions on severe COVID-19 when adjusted for multiple factors. As shown in Figure 3B, the presence of obesity and/or metabolic abnormalities may strengthen the impact of multiple conditions, including age, COPD, ischemic heart diseases, heart failure, liver cirrhosis, mania, bipolar disorder, depression, and sleep disorder, on severe COVID-19-related events in vaccinated patients (all $p < 0.05$). For example, in the COX regression model with adjusting confounding factors, ischemic heart disease (HR 2.97, 95% CI 2.24–3.95) was associated with an increased risk of severe COVID-19. The aHR for the effects of ischemic heart disease on severe COVID-19-related events fell to 1.61 (1.18–2.21) after we adjusted for all three metabolic abnormalities without obesity, and to 1.60 (1.16–2.19) after adjusting for all three metabolic abnormalities with obesity. Similar trends were also observed in the effects of other conditions on the risk of severe COVID-19-related events (Figure 3B). In addition, in unvaccinated individuals, the presence of obesity and/or metabolic abnormalities also reinforces the impact of multiple medical conditions, including age, asthma, COPD, ischemic heart disease, heart failure, mania, bipolar disorder, depression, and sleep disorder, on the occurrence of severe COVID-19-related events (Figure S3B). Obesity and metabolic abnormalities modulated approximately 50% of the excess risk of severe COVID-19 for individuals with various conditions in both vaccinated and unvaccinated participants, with the effect of ischemic heart disease most strongly modulated by more than 60% (the percentage of excess risk modulated [PERM] was 69.543 in vaccinated participants [Figure 3B] and 77.070 in unvaccinated participants [Figure S3B]).

Notably, the effect of obesity on severe COVID-19-related events decreased from 1.64 (1.30–2.08) to 1.32 (1.02–1.69) among vaccinated participants when we adjusted for all three metabolic abnormalities (Figure 4A). Similar results were seen among unvaccinated participants, where the effect of obesity on severe COVID-19 decreased from 2.13 (1.92–2.36) to 1.78 (1.59–1.98) when we adjusted for all three metabolic abnormalities, suggesting that metabolic abnormalities also moderate the effect of obesity on severe outcomes of COVID-19. Metabolic abnormalities moderated 50% of the excess risk of severe COVID-19 for individuals with obesity in vaccinated participants and 31% in unvaccinated participants. As shown in an upset plot (Figure 4B; Data S1), among the 288 vaccinated participants who experienced a severe COVID-19-related event, 115 were obese

Multivariate models adjusted for age, sex, race, smoking status, alcohol abuse/dependence, ischemic heart disease, and heart failure.
HR, hazard ratio; Ob, obesity; MA, metabolic abnormalities; Vaccinated(−)Ob_MA(−), non-vaccinated and have no obesity and metabolic abnormalities; Vaccinated(−)Ob_MA(+), non-vaccinated and have obesity or metabolic abnormalities; Vaccinated(+)Ob_MA(−), vaccinated and have no obesity and metabolic abnormalities; Vaccinated(+)Ob_MA(+), vaccinated and have obesity or metabolic abnormalities.

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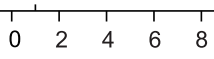
Characteristics	Severe COVID-19 outcomes (%)	Controls (%)	HR (95% CI)	P value
Vaccination dose 14 days before SARS-COV2 infection				
Two dose vs. One dose vaccined	210(3.4)	78(12.3)	0.28 (0.21, 0.36)	<0.0001
Age ≥ 65 vs. <65 (years)	247(6.4)	41(1.4)	4.58 (3.28, 6.40)	<0.0001
Male vs. Female	168(5.3)	120(3.3)	1.49 (1.17, 1.89)	0.0010
White vs. no-white	269(4.2)	18(5.0)	0.68 (0.42, 1.10)	0.1196
Current smoking	45(6.8)	240(4.2)	2.08 (1.47, 2.94)	<0.0001
Alcohol abuse/dependence	15(11.3)	273(4.1)	2.17 (1.26, 3.74)	0.0052
Obesity and metabolic disorders				
Overweight and obesity				
Overweight	108(3.9)	61(3.1)	1.02 (0.74, 1.41)	0.9107
Obesity	115(6.1)	169(3.5)	1.61 (1.17, 2.21)	0.0033
Hyperglycemia	63(10.2)	225(3.7)	2.05 (1.53, 2.74)	<0.0001
Prediabetes	17(8.4)	271(4.1)	1.54 (0.94, 2.52)	0.0866
Total Diabetes	46(11.1)	242(3.8)	2.14 (1.54, 2.98)	<0.0001
Type 1 diabetes	10(25.0)	278(4.1)	5.29 (2.78, 10.05)	<0.0001
Type 2 diabetes	36(9.6)	252(4.0)	1.74 (1.20, 2.50)	0.0031
Hyperlipidemia	132(8.9)	156(3.0)	2.08 (1.63, 2.65)	<0.0001
Hypertension	149(6.9)	139(3.0)	1.60 (1.26, 2.04)	0.0001
Comorbidity				
Asthma	55(5.5)	233(4.1)	1.37 (1.02, 1.84)	0.0387
COPD	35(19.7)	253(3.9)	2.99 (2.05, 4.37)	<0.0001
Chronic bronchitis	11(12.5)	277(4.2)	2.06 (1.09, 3.89)	0.0259
Interstitial lung disease	8(34.8)	280(4.2)	7.42 (3.63, 15.18)	<0.0001
Ischemic heart diseases	60(10.7)	228(3.7)	2.05 (1.53, 2.75)	<0.0001
Heart failure	9(23.7)	279(4.2)	3.70 (1.82, 7.52)	0.0003
Liver cirrhosis	8(21.6)	280(4.2)	3.52 (1.65, 7.49)	0.0011
CKD	14(18.2)	274(4.1)	2.91 (1.66, 5.09)	0.0002
Dementia	2(15.4)	286(4.2)	1.37 (0.33, 5.64)	0.6616
Mania, bipolar disorder, depression	37(6.6)	251(4.1)	1.51 (1.05, 2.16)	0.0250
Sleep disorder	45(7.1)	243(4.0)	1.63 (1.18, 2.27)	0.0034
Osteoarthritis	54(8.5)	234(3.8)	1.62 (1.19, 2.21)	0.0023
Immunodeficiency	1(11.1)	287(4.3)	2.31 (0.32, 16.56)	0.4047



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(39.9%), 149 had hypertension (51.7%), 132 had hyperlipidemia (45.8%), and 63 had hyperglycemia (21.9%). However, only 29 patients (10.1%) had obesity alone, 27 patients (9.4%) had hypertension alone, 18 patients (6.3) had hyperlipidemia alone, and 4 patients (1.4%) had hyperglycemia alone. Although isolated obesity, isolated hypertension, and isolated hyperlipidemia were significantly associated with a higher risk of severe COVID-19-related events among vaccinated and unvaccinated patients in multivariate COX regression analyses (Table S5; Data S1), most of the patients with obesity often had one to three metabolic abnormalities, which were also found in the unvaccinated patients (Figure 4C; Data S1), suggesting that we need to systematically assess the association of obesity and metabolic abnormalities with severe COVID-19-related events by incorporating the metabolic obesity phenotypes in both vaccinated and unvaccinated participants.

Metabolic abnormalities are modifiable factors for the risk of severe COVID-19 in the UK Biobank study

Four metabolic obesity phenotypes can be obtained by retyping obesity based on the status of metabolic abnormalities. The proportion of severe COVID-19-related events in the group with obesity and metabolic abnormalities was significantly higher than that in the group with metabolically healthy obesity (7.5 versus 3.9, $p < 0.05$; Figure 5A). When metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19 was higher than that of non-obese and metabolically normal people (Figure 5A). Similar results were also found when we assessed the risk of COVID-19-related hospitalization (Figure 5B) and death (Figure 5C), separately (all $p < 0.05$). As the number of metabolic abnormalities increased, the risk of severe clinical events increased significantly in both vaccinated (Figure 5A) and unvaccinated patients (Figures S4A–S4C). Nelson-Aalen curves and Kaplan-Meier curves demonstrated the same phenomenon in vaccinated (Figures 5D and 5E; Data S1) and unvaccinated patients (Figures S4D and S4E; Data S1), respectively.

In this study, participants who had a history of drug treatment in the 90 days prior to a SARS-COV-2 test were considered to have recently undergone drug therapy. As shown in Figure 6A, we found that the proportion of severe COVID-19-related events in the untreated hypertension group (7.7 versus 5.7 versus 3.0, $p < 0.001$), untreated hyperglycemia group (9.7 versus 8.1 versus 3.7, $p < 0.001$), untreated type 2 diabetes mellitus (T2DM) group (11.7 versus 7.8 versus 3.8, $p < 0.001$), and untreated hyperlipidemia group (9.4 versus 8.3 versus 3.0, $p < 0.001$) was higher than those in the corresponding treatment group and metabolic abnormalities-free control group. Multivariate COX regression analysis showed that untreated hypertension (aHR 1.58, 95% CI 1.19–2.12; $p = 0.002$), untreated hyperglycemia (aHR 1.57, 95% CI 1.02–2.43; $p = 0.042$), and untreated hyperlipidemia (aHR 2.04, 95% CI 1.50–2.77; $p < 0.001$) were risk factors for severe COVID-19-related events in vaccinated participants; however, medicated hypertension (aHR 1.10, 95% CI 0.76–1.59; $p = 0.610$), medicated hyperglycemia (aHR 1.28, 95% CI 0.82–2.00; $p = 0.279$), and medicated T2DM (aHR 1.15, 95% CI 0.70–1.88; $p = 0.579$) were no longer risk factors for COVID-19-related hospitalization (Figure 6B). In addition, we found that among vaccinated patients with metabolic abnormalities, those treated with antihypertensive therapy (aHR 0.64, 95% CI 0.48–0.86; $p = 0.003$), lipid-lowering therapy (aHR 0.50, 95% CI 0.37–0.68; $p < 0.001$), or glucose-lowering therapy (aHR 0.55, 95% CI 0.36–0.83; $p = 0.004$) had a reduced risk of COVID-19-related hospitalization compared with untreated patients after adjusting for age, sex, race, smoking status, alcohol abuse/dependence, obesity, pharmacological intervention for metabolic abnormalities (antihypertensive therapy, hypoglycemic therapy, or lipid-lowering therapy), ischemic heart disease, and heart failure.

It is important to note that we also obtained consistent results in unvaccinated patients (Figure 6B), suggesting that antihypertensive, glucose-lowering, and lipid-lowering treatments each play an important role in improving the outcomes of severe COVID-19 regardless of vaccination status. As the total number of deaths among vaccinated patients was small ($n = 48$), we only assessed the impact of drug intervention on the risk of hospitalization in vaccinated patients. Notably, we found similar trends for the effect of drug intervention on the risk of COVID-19-related hospitalization in vaccinated patients (Figure 6B) and COVID-19-related hospitalization and death in unvaccinated patients (Table S6). By Nelson-Aalen and Kaplan-Meier analyses we found that the impact of antihypertensive (Figure S5B; Data S1), glucose-lowering (Figures S5C and S5D; Data S1), and lipid-lowering therapy (Figure S5E; Data S1) was associated with a lower cumulative incidence of COVID-19-related hospitalizations in vaccinated patients and COVID-19-related death in unvaccinated patients (Figures S6A–S6D; Data S1) with metabolic abnormalities, respectively.

Obesity and metabolic abnormalities and the risk of severe COVID-19 in the NHIS study

To further validate our study, we utilized the NHIS database for a similar analysis as that above for the data from the UK Biobank. In the cross-sectional study based on data from NHIS, a total of 29,482 adults had relevant questionnaire information in the 2021 NHIS. Of these people, 3,494 (11.9%) were confirmed to have COVID-19. After excluding pregnant participants and patients with missing data on study variables, 2,588 participants who tested positive for COVID-19 were included in the analysis, of whom 1,752 (67.7%) had been vaccinated against COVID-19 and 572 (65.2%) received two or more doses of vaccine. A total of 533 (20.6%) participants experienced severe COVID-19 symptoms. Due to the limitations of the NHIS, we cannot determine the sequence of vaccination and the onset of COVID-19 infection, so we could not explore the impact of obesity and metabolic abnormalities on the protective efficacy of COVID-19 vaccine against severe COVID-19 symptoms. However, data from NHIS can be used to assess the association between obesity and metabolic abnormalities and the risk of severe COVID-19 symptoms.

Figure 2. The associations of demographic and clinical characteristics with severe COVID-19 outcomes in participants who received one or more doses of vaccine 14 days or earlier before SARS-CoV-2 infection

Multivariate models adjusted for age, sex, race, smoking status, alcohol abuse/dependence, vaccine dose, obesity, hypertension, hyperglycemia, and hyperlipidemia. HR, hazard ratio; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney diseases.

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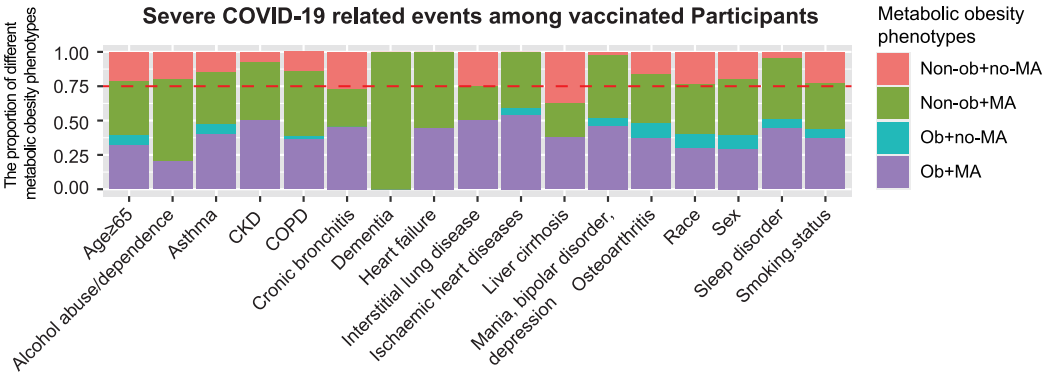

B

Characteristics	HR (95% CI)	P1 value	F value	P2 value		PERM
Age≥ 65 vs. <65 (years)						
Confounders-adjusted	4.55 (3.27, 6.33)	<0.001				
Adjusted for three metabolic disorders	3.48 (2.47, 4.89)	<0.001	10.875	0.001	*	30.141
Adjusted for obesity and metabolic disorders	3.50 (2.49, 4.92)	<0.001	7.482	0.006	*	29.588
Male vs. Female						
Confounders-adjuste	1.60 (1.27, 2.03)	<0.001				
Adjusted for three metabolic disorders	1.40 (1.10, 1.77)	0.005	1.574	0.210		33.333
Adjusted for obesity and metabolic disorders	1.40 (1.11, 1.78)	0.005	3.273	0.070		33.333
Current smoking						
Confounders-adjuste	1.73 (1.26, 2.37)	0.001				
Adjusted for three metabolic disorders	1.69 (1.23, 2.32)	0.001	1.487	0.226		—
Adjusted for obesity and metabolic disorders	1.70 (1.24, 2.34)	0.001	0.06	0.942		—
Alcohol abuse/dependence						
Confounders-adjuste	2.82 (1.68, 4.74)	<0.001				
Adjusted for three metabolic disorders	2.42 (1.44, 4.07)	0.001	2.898	0.089		—
Adjusted for obesity and metabolic disorders	2.41 (1.43, 4.06)	0.001	1.146	0.284		—
Comorbidity						
Asthma						
Confounders-adjuste	1.36 (1.01, 1.82)	0.042				
Adjusted for three metabolic disorders	1.21 (0.90, 1.63)	0.196	3.261	0.071		—
Adjusted for obesity and metabolic disorders	1.20 (0.89, 1.61)	0.231	1.758	0.185		—
COPD						
Confounders-adjuste	5.41 (3.80, 7.70)	<0.001				
Adjusted for three metabolic disorders	3.55 (2.47, 5.11)	<0.001	6.758	0.009	*	42.177
Adjusted for obesity and metabolic disorders	3.54 (2.46, 5.09)	<0.001	7.863	0.005	*	42.404
Ischemic heart diseases						
Confounders-adjuste	2.97 (2.24, 3.95)	<0.001				
Adjusted for three metabolic disorders	1.61 (1.18, 2.21)	0.003	2.566	0.009	*	69.036
Adjusted for obesity and metabolic disorders	1.60 (1.16, 2.19)	0.004	8.053	0.005	*	69.543
Heart failure						
Confounders-adjuste	6.32 (3.25, 12.28)	<0.001				
Adjusted for three metabolic disorders	3.05 (1.55, 6.00)	0.001	4.434	0.035	*	61.466
Adjusted for obesity and metabolic disorders	3.04 (1.54, 5.98)	0.001	3.265	0.071	*	61.654
Liver cirrhosis						
Confounders-adjuste	5.44 (2.69, 10.98)	<0.001				
Adjusted for three metabolic disorders	3.80 (1.88, 7.69)	<0.001	6.612	0.010	*	36.937
Adjusted for obesity and metabolic disorders	3.75 (1.85, 7.58)	<0.001	9.191	0.002	*	38.063
CKD						
Confounders-adjuste	4.61 (2.70, 7.89)	<0.001				
Adjusted for three metabolic disorders	2.30 (1.32, 3.99)	0.003	0.082	0.774		—
Adjusted for obesity and metabolic disorders	2.27 (1.31, 3.95)	0.004	2.755	0.097		—
Mania, bipolar disorder, depression						
Confounders-adjuste	1.65 (1.17, 2.32)	0.005				
Adjusted for three metabolic disorders	1.32 (0.93, 1.87)	0.118	12.325	<0.001	*	50.769
Adjusted for obesity and metabolic disorders	1.29 (0.91, 1.83)	0.157	9.338	0.002	*	55.385
Sleep disorder						
Confounders-adjuste	1.82 (1.32, 2.50)	<0.001				
Adjusted for three metabolic disorders	1.40 (1.02, 1.94)	0.039	10.907	0.001	*	51.220
Adjusted for obesity and metabolic disorders	1.37 (0.99, 1.89)	0.059	9.076	0.003	*	54.878
Osteoarthritis						
Confounders-adjuste	2.23 (1.66, 3.00)	<0.001				
Adjusted for three metabolic disorders	1.73 (1.28, 2.33)	<0.001	0.467	0.494		—
Adjusted for obesity and metabolic disorders	1.70 (1.25, 2.30)	<0.001	0.582	0.446		—

Figure 3. Metabolic moderators of the effects of multiple conditions on the risk of severe COVID-19 in vaccinated participants

(A) The proportion of obesity and metabolic abnormalities among various risk factors for severe COVID-19-related events among vaccinated patients.

(B) Hazard ratio for multiple conditions was adjusted for obesity and metabolic abnormalities in severe COVID-19-related events in vaccinated participants.

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Regardless of COVID-19 vaccination status, participants with obesity (25.9% versus 17.5%, $p < 0.001$), hypertension (26.3% versus 17.7%, $p < 0.001$), hyperlipidemia (26.6% versus 18.3%, $p < 0.001$), or hyperglycemia (26.5% versus 19.9%, $p = 0.011$) had significantly higher proportions of severe COVID-19 symptoms than those without obesity or metabolic abnormalities. We found similar effects of obesity and metabolic abnormalities on the risk of severe COVID-19-related events in both the UK Biobank and NHIS databases. When metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19 was higher than that of non-obese and metabolically normal people (all $p < 0.05$; Table S7). As the number of metabolic abnormalities increased, the risk of severe COVID-19 symptoms increased significantly (all $p < 0.05$; Table S7). In addition, consistent with the overall findings above, obesity and metabolic abnormalities had similar associations with the risk of severe COVID-19 symptoms when analyzed separately among vaccinated and unvaccinated participants (all $p < 0.05$; Table S8).

DISCUSSION

We have identified a range of risk factors for severe COVID-19 in individuals from England who were previously vaccinated, which is dominated by obesity and metabolic abnormalities. Notably, in addition to age and sex, patients with modifiable risk factors, such as obesity and metabolic abnormalities, had the highest proportion of severe COVID-19-related events. What is more, when metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19-related events is higher than that of non-obese and metabolically normal people. As the number of metabolic abnormalities increased, the risk of severe COVID-19-related events increased significantly. Most important, pharmacological interventions were significantly associated with a reduced risk of COVID-19-related hospitalization and death in both vaccinated and unvaccinated patients with metabolic abnormalities, particularly those with hypertension and hyperglycemia.

To our knowledge, this is the first study to systematically elucidate the association between obesity, metabolic abnormalities, and the risk of COVID-19 hospitalization and death in vaccinated patients since the launch of the COVID-19 vaccination program, as well as the role of pharmacological interventions targeting metabolic abnormalities in the risk of severe COVID-19-related events. The innovation of this study is to identify the modifiable factors that may affect the protective efficacy of COVID-19 vaccine use against the occurrence of severe COVID-19-related events, so the management and treatment of these risk factors should be focused on when implementing vaccination programs. Moreover, the study has two key strengths. First, we utilized data from a detailed and long-term prospective health database, which included comprehensive information on linked vaccination, primary care, RT-PCR testing, hospitalization, and mortality records. Second, we not only evaluated the association between obesity, metabolic abnormalities, and the risk of severe COVID-19, but also obtained drug prescription information from the primary care database to evaluate the effect of drug interventions targeting metabolic abnormalities on the risk of severe COVID-19.

As reported in studies published before the advent of COVID-19 vaccines, obesity and metabolic abnormalities were associated with an increased risk of onset, progression, and outcome of COVID-19.[4,7,23] Patients with obesity, diabetes, hypertension, or hyperlipidemia are often in a chronic inflammatory state, which may lead to a weakened immune response to infectious agents and thus to a greater susceptibility to infection.[4,7,23] In addition, obesity and metabolic abnormalities are associated with a reduced immunogenicity in response to vaccination for infectious diseases, such as hepatitis B, tetanus, and influenza vaccines.[24,25] Two studies, published in September and December 2021, found that T2DM was associated with a risk of severe COVID-19 outcomes in vaccinated patients.[13,14] In this study, we found that the COVID-19 vaccines were less effective in patients with multiple metabolic conditions (such as obesity, hypertension, diabetes, and hyperlipidemia) than in people with none or only a few metabolic conditions, and the risk for severe COVID-19 could be partially alleviated by pharmacological interventions targeting these metabolic abnormalities. These associations may arise because obesity and metabolic abnormalities often co-exist with multiple factors that increase the risk of more severe symptoms and death from many infectious diseases.[4] Studies on COVID-19 vaccines from the US[5] and Israel[26] have found that COVID-19 infections post-vaccination tend to occur in the presence of multiple comorbidities, such as excess body weight, diabetes, hypertension, and cardiovascular disease. Other specific mechanisms of SARS-CoV-2 infection associated with obesity and metabolic abnormalities, such as a compromised immune response and hyper-inflammatory systemic responses,[4,7,24] also need to be considered separately, which may have clinical implications for preventing disease progression and improving management of patients with SARS-CoV-2 infection.

We noted that obesity and metabolic abnormalities explained approximately 50% of the excess risk of severe COVID-19-related events for individuals with common risk factors. In addition, metabolic abnormalities also modulated the effect of obesity on severe outcomes of COVID-19. This finding suggests that clinical interventions that control blood pressure, glucose levels, and cholesterol may go some way to addressing the excess risk of severe COVID-19-related events in participants with multiple chronic diseases. In fact, we did find here that pharmacological interventions targeting metabolic abnormalities reduced the risk of severe COVID-19-related events in vaccinated and unvaccinated patients as well.

Recently, Piernas et al. investigated the association between BMI and COVID-19 vaccine intake, vaccine effectiveness, and

P1 values reflect the results of Cox regression model analysis; P2 values reflect the results of the moderating effect analysis; *$p < 0.05$ was considered significant. The F value reflects the strength of the moderating effect, and the higher the F value, the greater the moderating effect. Adjustment for confounders including age, sex, race, smoking status, and alcohol abuse/dependence.
HR, hazard ratio; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney diseases.

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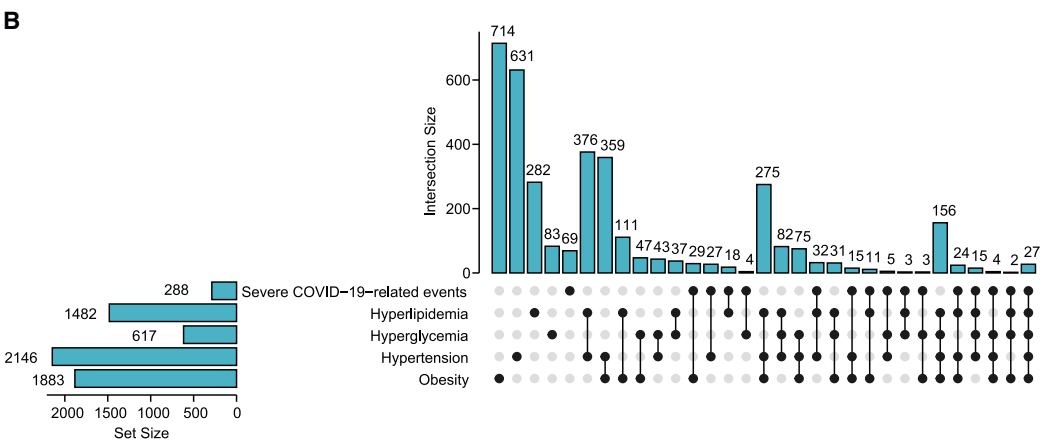
Obesity	Severe COVID-19 outcomes (%)	Controls (%)	HR (95% CI)	P value
Vaccinated participants	115(6.1)	173(3.6)		
Confounders−adjusted			1.64(1.30−2.08)	<0.001
Adjusted for metabolic disorders				
One metabolic disorders				
Hypertension			1.48(1.16−1.89)	0.002
Hyperglycemia			1.48(1.16−1.89)	0.002
Hyperlipidemia			1.44(1.13−1.84)	0.003
Two metabolic disorders				
Hypertension and hyperlipidemia			1.39(1.09−1.78)	0.009
Hyperglycemia and hypertension			1.38(1.07−1.77)	0.013
Hyperglycemia and hyperlipidemia			1.36(1.06−1.74)	0.016
Three metabolic disorders			1.32(1.02−1.69)	0.032
Unvaccinated participants	709(16.9)	728(7.7)		
Confounders−adjusted			2.13(1.92-2.36)	<0.001
Adjusted for metabolic disorders				
One metabolic disorders				
Hypertension			1.93(1.74−2.15)	<0.001
Hyperglycemia			1.94(1.74−2.16)	<0.001
Hyperlipidemia			1.93(1.73−2.14)	<0.001
Two metabolic disorders				
Hypertension and hyperlipidemia			1.85(1.66−2.06)	<0.001
Hyperglycemia and hypertension			1.82(1.63−2.03)	<0.001
Hyperglycemia and hyperlipidemia			1.83(1.640−2.04)	<0.001
Three metabolic disorders			1.78(1.59−1.98)	<0.001



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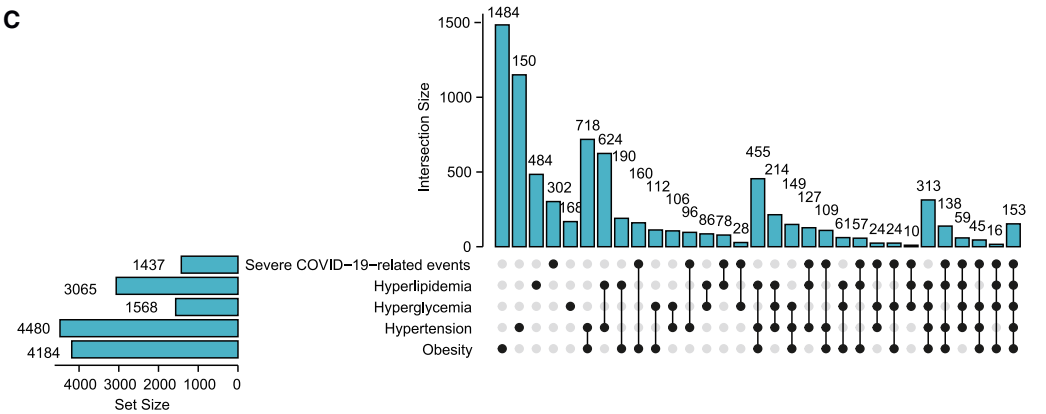

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the risk of severe COVID-19 outcomes after vaccination.[15] They found that vaccines were slightly less effective in individuals with obesity. Similar results were also found in our study. Nonetheless, it is worth noting that we found that metabolic abnormalities mediate the impact of obesity on the severe consequences of COVID-19. When we adjusted for all three metabolic abnormalities (hyperglycemia, hyperlipidemia, and hypertension), the impact of obesity on severe COVID-19-related events was significantly reduced, making our results and conclusions distinct from those of Piernas et al. In addition, when metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19 was higher than that of non-obese and metabolically normal people, suggesting metabolic abnormalities rather than obesity per se may have a greater impact on vaccine efficacy. Further, the purpose of our study was to identify core modifiable risk factors for severe COVID-19 to more effectively promote early intervention as a strategy to minimize the risk of severe COVID-19 (i.e., hospitalizations and deaths) in vaccinated individuals. In our study, not only did we find that metabolic abnormalities are indeed modifiable risk factors for severe COVID-19 in both vaccinated and unvaccinated individuals, but we also found that pharmacological interventions targeting these abnormalities were significantly associated with a reduced risk of this outcome. So in summary, while at first glance the focus and the results of the Piernas et al. study may seem quite similar to ours, in actuality we feel our study is quite distinct as it comes to slightly different conclusions, but more importantly offers a roadmap going forward as to how to avoid the higher risk of severe COVID-19 in non-vaccinated and vaccinated individuals.

Given the COVID-19 global pandemic and the presence of post-vaccine breakthrough SARS-CoV-2 infections, the role of obesity and metabolic abnormalities in promoting the risk of COVID-19-related hospitalizations and death in vaccinated participants needs to be taken very seriously. This issue is particularly important because obesity, hyperlipidemia, diabetes, and hypertension were associated with an elevated risk of severe COVID-19-related events, and drug interventions targeting underlying metabolic abnormalities may have significant health benefits among individuals with COVID-19. Therefore, to better combat the COVID-19 pandemic, weight loss and the improvement of hypertension, hyperglycemia, and hyperlipidemia should be promoted. Furthermore, clinical staff should focus on the health management of patients with obesity and metabolic abnormalities and advocate for patients to receive medical intervention as soon as possible, which will improve the quality of life and promote a healthier lifestyle.

Limitations of study

While our study has many strengths as outline above, we need to acknowledge that there are still a few limitations. First, data on participants' characteristics, such as occupation, social activities, home address, education level, and socioeconomic status, which are closely related to the risk of COVID-19 infection, were collected 10 years ago and may have changed since then. Thus, we did not evaluate these risk factors for the post-vaccine breakthrough COVID-19 infections in this study. As vaccinated patients tend to be asymptomatic carriers of SARS-CoV-2 infection and only a small number of patients are at risk of hospitalization and death, we focused on assessing the more important issue of risk factors for hospitalization and death in vaccinated patients in this study. Second, as the UK Biobank does not provide detailed laboratory test information of participants at the time of vaccination, we mainly relied on ICD10 codes to determine obesity and metabolic abnormalities, which makes it difficult to grade the severity of obesity and metabolic abnormalities. Third, as the total number of deaths among vaccinated patients was small, we only assessed the impact of drug intervention on the risk of hospitalization. Notably, we found similar results for the effect of drug intervention on the risk of death in unvaccinated patients, reflecting the robustness of our study. Fourth, in the study based on data from the 2021 NHIS, we were unable to determine the order of COVID-19 infection and vaccination, and we were only able to roughly assess the association of obesity and metabolic abnormalities with severe COVID-19 symptoms in both vaccinated and unvaccinated populations. Notably, despite differences in population, data structure, and COVID-19-related clinical events between the NHIS database and UK Biobank database, we found similar effects of obesity and metabolic abnormalities on the risk of severe COVID-19-related events in vaccinated patients in both databases. When metabolic abnormalities were present, regardless of obesity, the risk of severe COVID-19 was higher than that of non-obese and metabolically normal people in vaccinated and unvaccinated patients in both databases. Last, as the UK Biobank does not provide detailed information about the dose and duration of drug use, as well as the effect of drug therapy on disease control, we did not evaluate the dose-time effect of drug intervention for metabolic abnormalities on the risk of severe COVID-19. However, preliminarily we found that patients with metabolic abnormalities who had pharmacological interventions for their metabolic complications had a reduced risk of severe COVID-19. In view of these limitations, further studies with more detailed cohort data are needed in the future.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
  - Study design and data sources

Figure 4. Obesity, metabolic abnormalities, and severe COVID-19-related events in vaccinated and unvaccinated participants

(A) Hazard ratios for obesity were adjusted for different combinations of metabolic abnormalities in severe COVID-19-related events.

(B and C) The upset plots showed the coexistence of obesity, metabolic abnormalities, and severe COVID-19-related events in vaccinated (B) and unvaccinated participants (C).

HR, hazard ratio.

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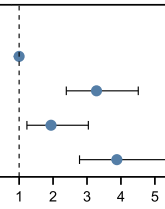
CellPress

A

Characteristics	N (%)	Severe COVID-19 outcomes (%)	HR (95% CI)	P value
Metabolic obesity phenotypes				
Non−ob + no MA	3228(47.8)	69(2.1)		
Non−ob + MA	1638(24.3)	104(6.3)	1.75(1.27−2.43)	0.001
Ob + no MA	743(11.0)	29(3.9)	1.81(1.17−2.81)	0.008
Ob + MA	1140(16.9)	86(7.5)	1.99(1.41−2.83)	<0.001
Metabolic obesity groups				
Non−ob + no MA	3228(47.8)	69(2.1)	1	
Non−ob + one MA	1045(15.5)	49(4.7)	1.56(1.07−2.27)	0.021
Non−ob + two MA	496(7.3)	40(8.1)	1.91(1.26−2.9)	0.002
Non−ob + three MA	97(1.4)	15(15.5)	3.29(1.79−6.06)	<0.001
Ob + no MA	743(11.0)	29(3.9)	1.82(1.17−2.82)	0.007
Ob + one MA	546(8.1)	29(5.3)	1.84(1.18−2.86)	0.007
Ob + two MA	411(6.1)	30(7.3)	1.76(1.10−2.81)	0.019
Ob + three MA	183(2.7)	27(14.8)	3.34(2.01−5.56)	<0.001

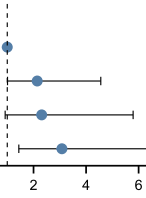
B

Characteristics	HR (95% CI)	P value
Metabolic obesity phenotypes		
Non−ob + no MA	1	
Non−ob + MA	3.28 (2.39, 4.51)	<0.001
Ob + no MA	1.94 (1.23, 3.04)	0.004
Ob + MA	3.88 (2.78, 5.42)	<0.001



C

Characteristics	HR (95% CI)	P value
Metabolic obesity phenotypes		
Non−ob + no MA	1	
Non−ob + MA	2.14 (1.01, 4.56)	0.048
Ob + no MA	2.31 (0.92, 5.79)	0.074
Ob + MA	3.08 (1.44, 6.54)	0.004



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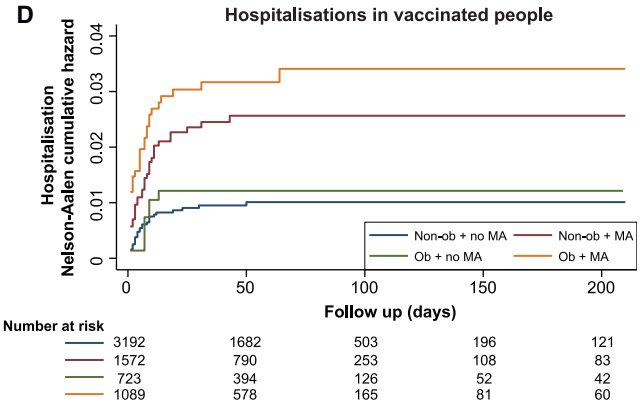
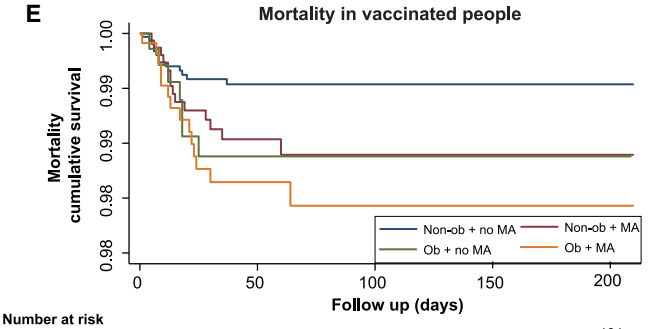


Number at risk

3192	1682	503	196	121
1572	790	253	108	83
723	394	126	52	42
1089	578	165	81	60

E



Number at risk

3227	1719	521	207	131
1638	845	281	126	96
743	406	133	55	45
1139	632	186	94	73

Figure 5. Metabolic obesity phenotypes and the risk of severe COVID-19

(A) The association between different metabolic obesity phenotypes and the risk of severe COVID-19 in vaccinated participants.

(B and C) The association between different metabolic obesity phenotypes and the risk of COVID-19 hospitalizations (B) and deaths (C) in vaccinated participants.

(D and E) Nelson-Aalen curves and Kaplan-Meier curves demonstrating the cumulative incidence of COVID-19-related hospitalizations (D) and deaths (E) for metabolic obesity phenotypes in vaccinated patients.

Multivariate models adjusted for age, sex, race, smoking status, alcohol abuse/dependence, vaccine dose, and comorbidities (asthma, COPD, chronic bronchitis, interstitial lung disease, ischemic heart disease, heart failure, liver cirrhosis, CKD, dementia, mania, bipolar disorder, depression, sleep disorders, and osteoarthritis).

HR, hazard ratio; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney diseases; Ob, obesity; MA, metabolic abnormalities.

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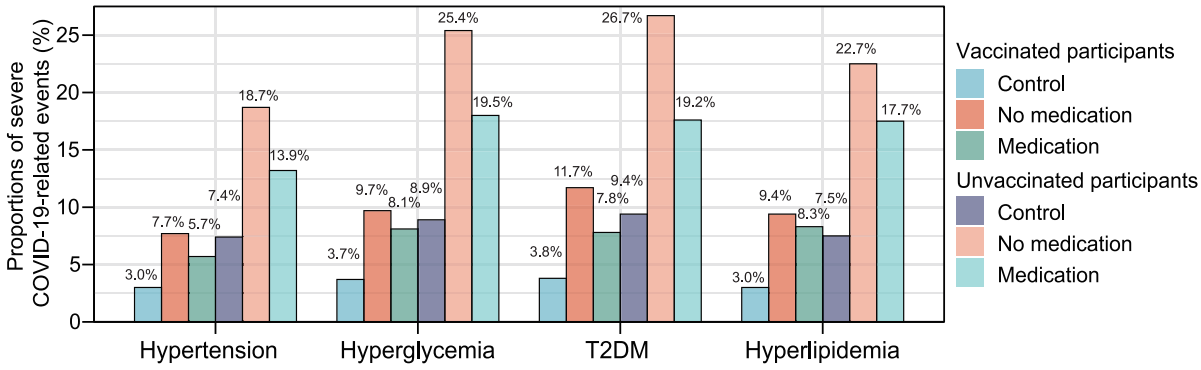
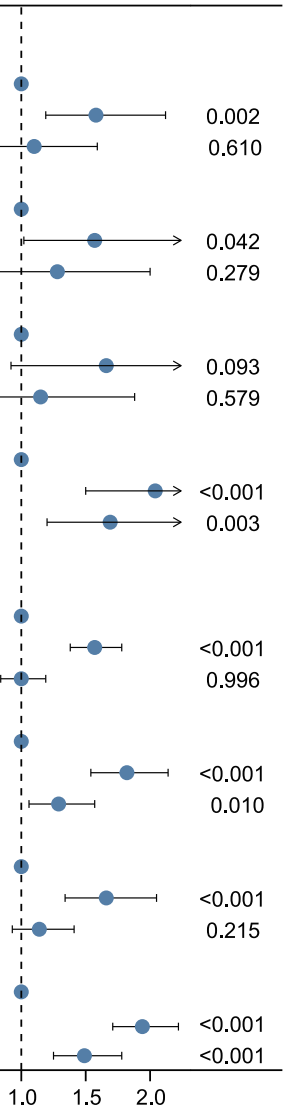
A



B

Metabolic abnormalities	N (%)	Severe COVID-19 outcomes (%)	HR (95% CI)	P value
Vaccinated participants				
Hypertension				
No hyperglycemia	4603(68.2)	139(3.0)	1	
No medication	1332(19.7)	103(7.7)	1.58(1.19–2.12)	0.002
Medication	814(12.1)	46(5.7)	1.10(0.76–1.59)	0.610
Hyperglycemia				
No hyperglycemia	6132(91.6)	225(3.7)	1	
No medication	267(4.0)	26(9.7)	1.57(1.02–2.43)	0.042
Medication	298(4.4)	24(8.1)	1.28(0.82–2.00)	0.279
T2DM				
No T2DM	6334(94.6)	242(3.8)	1	
No medication	120(1.8)	14(11.7)	1.66(0.92–3.01)	0.093
Medication	243(3.6)	19(7.8)	1.15(0.70–1.88)	0.579
Hyperlipidemia				
No hyperlipidemia	5267(78.0)	156(3.0)	1	
No medication	797(11.8)	75(9.4)	2.04(1.50–2.77)	<0.001
Medication	685(10.1)	56(8.3)	1.69(1.20–2.38)	0.003
Unvaccinated participants				
Hypertension				
No hypertension	9133(67.1)	675(7.4)	1	
No medication	2921(21.5)	545(18.7)	1.57(1.38–1.78)	<0.001
Medication	1559(11.5)	217(13.9)	1.00(0.84–1.19)	0.996
Hyperglycemia				
No hyperglycemia	12044(89.2)	1066(8.9)	1	
No medication	737(5.5)	187(25.4)	1.82(1.54–2.14)	<0.001
Medication	728(5.4)	142(19.5)	1.29(1.06–1.57)	0.010
T2DM				
No T2DM	12520(92.7)	1176(9.4)	1	
No medication	386(2.9)	103(26.7)	1.66(1.34–2.05)	<0.001
Medication	603(4.5)	116(19.2)	1.14(0.93–1.41)	0.215
Hyperlipidemia				
No hyperlipidemia	10548(77.5)	793(7.5)	1	
No medication	2033(14.9)	461(22.7)	1.94(1.71–2.22)	<0.001
Medication	1032(7.6)	183(17.7)	1.49(1.25–1.78)	<0.001



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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2023.02.016.

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AUTHOR CONTRIBUTIONS

X.F. and J.H. had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, J.Z., Y. Song, X.F., and J.H.; acquisition, analysis, or interpretation of data, all authors; drafting of the manuscript, X.F. and J.H.; critical revision of the manuscript for important intellectual content, Y.C., D.W., P.L., E.Z., T.L., Q.L., Y. Shi, J.F., Z. Yao, K.L.P., Z. Yuan, Z.W., Y. Song, and J.Z.; statistical analysis, X.F., J.H., J.F., E.Z., and Z. Yuan; funding acquisition, J.Z., Y. Song, X.F., and Z.W.; administrative, technical, or material support, J.Z. and Y. Song; supervision, J.Z. and Y. Song.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Figure 6. Pharmacological interventions for metabolic abnormalities and the risk of severe COVID-19-related events in vaccinated and unvaccinated participants

(A) Proportion of severe COVID-19-related events in the treatment group, the nontreatment group with metabolic abnormalities, and the metabolic abnormalities-free control group.

(B) Association of pharmacologic interventions targeting metabolic abnormalities with risk for severe COVID-19-related events.

Multivariate models adjusted for age, sex, race, smoking status, alcohol abuse/dependence, obesity, blood pressure-lowering therapy, glucose-lowering therapy, lipid-lowering therapy, ischemic heart disease, and heart failure. HR, hazard ratio; T2DM, type 2 diabetes mellitus.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
The UK Biobank data	UK Biobank Limited	https://www.ukbiobank.ac.uk/
Main dataset	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access
COVID-19 test results	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
Primary care data	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
Hospital inpatient data	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
Death data	UK Biobank Limited	https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data
The 2021 National Health Interview Survey	The United States Centers for Disease Control and Prevention	https://www.cdc.gov/nchs/nhis/2021nhis.htm
Data S1 source data	This study	https://doi.org/10.17632/ht6w2ndk46.1
Software and algorithms		
R-4.0.2	R Foundation for Statistical Computing	https://www.r-project.org/
STATA 16.0	StataCorp LLC	https://www.stata.com/
MySQL 8.0.32	MySQL AB	https://www.mysql.com/cn/
Adobe illustrator CC 2019	Adobe company	https://www.adobe.com/cn
upSetR_1.4.0	Jake Conway et al.	https://cran.r-project.org/web/packages/UpSetR/index.html
ggplot2_3.4.0	Hadley Wickham et al.	https://cran.r-project.org/web/packages/ggplot2/index.html
haven_2.5.1	Hadley Wickham et al.	https://cran.r-project.org/web/packages/haven/index.html
dplyr_1.1.0	Hadley Wickham et al.	https://cran.r-project.org/web/packages/dplyr/index.html
plyr_1.8.8	Hadley Wickham et al.	https://cran.r-project.org/web/packages/plyr/index.html
tidyverse_1.3.2	Hadley Wickham et al.	https://cran.rproject.org/web/packages/tidyverse/index.html

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to the Lead Contact, Jiajun Zhao (jjzhao@sdu.edu.cn).

Materials availability

No new reagents or materials were generated in this study.

Data and code availability

This study used data from the UK Biobank (application number 89483). For details, please contact access@ukbiobank.ac.uk. All other data are contained in the article and its supplementary information or available upon reasonable request. All values used to generate the figures of the paper can be found in the file Data S1, related to Figures 1A, 3A, 4B, 4C, 5D, 5E, S2, S3A, S4D, S4E, S5, and S6. The Data S1 source data and the data from 2021 NHIS are available from Mendeley Data at https://doi.org/10.17632/ht6w2ndk46.1.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study design and data sources

A prospective cohort study was conducted using data from the UK Biobank cohort, a national health resource that involved the recruitment of more than 500,000 participants aged 40–69 during 2006–2010 from 22 centers in England (89%), Scotland (7%) and Wales (4%).[27] A mass COVID-19 vaccination plan in UK was launched in Dec. 8, 2020, which first deployed the BNT162b2

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vaccine, followed by the ChAdOx1 and mRNA-1273 vaccines.[28] All participants from England provided comprehensive information on linked vaccination, primary care, RT-PCR testing, hospitalization, and mortality records. The initial protocol of the UK Biobank study is available (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf), which has ethical approval from its own Ethics Advisory Committee (EAC) (https://www.ukbiobank.ac.uk/ethics/). The participants gave informed consent and public involvement are detailed online (https://www.ukbiobank.ac.uk/learn-more-aboutuk-biobank). This project was granted under the application of 89,483.

In addition, to further observe the impact of obesity and metabolic abnormalities on the risk of severe COVID-19-related events from different populations, data from the 2021 National Health Interview Survey were used for the current study (https://www.cdc.gov/nchs/nhis/2021nhis.htm). The study design based on NHIS data was a cross-sectional study. The NHIS is a nationally representative household survey of the non-hospitalized population in the United States and is conducted continuously throughout the year by the National Center for Health Statistics (NCHS). The main objective of the NHIS is to monitor the health of the United States population through the collection and analysis of data on a broad range of health topics. In the 2021 NHIS survey, detailed information about COVID-19 was collected, including vaccination status, SARS-CoV-2 infection status, and severity of COVID-19 symptoms.

Participants

Participants from England were selected, as vaccination data for Scotland and Wales were not available in UK Biobank. We utilized data from 113,336 participants aged 50 years or older who received SARS-CoV-2 tests, including 54,319 individuals vaccinated with one or more doses of BNT162b2 or ChAdOx1 14 days or more after their first dose on Dec. 8, 2020. Individuals were followed from the point of receiving their first dose of the BNT162b2 or ChAdOx1 COVID-19 vaccines until hospital admission, or death due to COVID-19, or the end of the study period on Oct. 18, 2021. All participants provided comprehensive information on sociodemographic, lifestyle, and health-related factors, which has been described in detail elsewhere. The UK Biobank began releasing COVID-19 test results from March 16, 2020 (https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/covid-19-data). Several external data sources have been linked to UK Biobank to enable COVID-19 research, including COVID-19 tests from Public Health England (PHE), hospital inpatient data from Hospital Episode Statistics (HES), primary care data provided directly by the system suppliers (TPP, https://www.tpp-uk.com/or EMIS, https://www.emishealth.com/), and mortality data.

In the 2021 NHIS, there were 29,482 adults completed interviews with a response rate of 50.9%. Of these people, 3494 (11.9%) were confirmed to have COVID-19. After excluding participants pregnancy and with missing data on study variables, 2588 participants were included in the analysis, of whom 1752 (67.7%) had been vaccinated against COVID-19, but the timing of SARS-CoV-2 test was unclear due to survey limitations.

METHOD DETAILS

Classification of vaccination status

Participants were considered vaccinated if they received one or more doses of vaccine 14 days or earlier before SARS-CoV-2 testing. Participants were considered as unvaccinated if they had never been vaccinated or received their first dose within 14 days before testing (Figures S1A and S1B). Participants were considered fully vaccinated after receiving the second dose prior to 14 days before testing.[2,29] Participants were considered not fully vaccinated if they had never received a second dose of vaccine or had received their second dose within 14 days before testing (Figure S1C). Previous studies have found no difference in the protection against infection between BNT162b2 and ChAdOx1vaccines.[2,14,28] A small number of people who received the mRNA-1273 vaccine (n = 14) were excluded. Vaccination data was obtained from primary care prescription records, including the vaccine brand and the date of receipt of each dose. The dm+d codes (a dictionary of medicines and devices used across the UK's National Health Service) were used to identify these vaccines, and the relevant codes are shown in Table S9.

In the 2021 NHIS, participants were asked three main questions ''Have you had a COVID-19 vaccination?'', ''How many COVID-19 vaccinations have you received?'', and ''Month/Year of most recent COVID-19 vaccination''. Based on participants' answers (''Yes'' or ''No'') to the above questions, we were able to obtain the number and timing of vaccinations.

Ascertainment of exposure factors

The primary exposure factors were obesity and metabolic abnormalities, including hyperglycemia (prediabetes, Type 1 diabetes mellitus (DM), and Type 2 DM), hypertension, and hyperlipidemia. To determine whether participants were overweight or obese, we used the body mass index (BMI) at enrollment (BMI 25.0–29.9, overweight; 30.0 and Above, Obesity), combined with diagnosis data and death registry records linked to the UK Biobank according to ICD-10 (the 10th revisions of the International Classification of Diseases). Because the participants' initial BMI was measured between 2006 and 2010, their BMI could have changed over time, so we combined the latest available data of clinical diagnosis of overweight and obesity with initially reported BMI to determine the overweight and obesity status. For example, if a participant's initial BMI at enrollment was in the normal range, but at the latest clinical diagnosis after enrollment it was in the overweight or obese range, we categorized that participant as being overweight or obese to ensure that our pool of participants with overweight or obesity was correct. Prediabetes was defined as no self-reported diabetes, and percent hemoglobin A1c (%HbA1c) between 6 and 6.4 (42–47 mmol/L) and/or hospital records of prediabetes. Since the participants' initial %HbA1c was measured between 2006 and 2010, their %HbA1c could have changed over time, so we combined that information with the latest information of clinical diagnosis of prediabetes after enrollment and %HbA1c to determine

prediabetes. For example, patients with an initial %HbA1c in the normal range, but who had clinical diagnosis of prediabetes after enrollment, was diagnosed as prediabetic in our analysis to ensure that our pool of patients with prediabetes was correct. For diabetes, this condition was based on a self-reported history of diabetes (type 1 or type 2 diabetes) or self-reported use of insulin or hospital records of diabetes. Incident hypertension and hyperlipidemia was ascertained based on self-reported history, hospital admission and diagnosis data and death registry records linked to the UK Biobank. The ICD code and UK Biobank Field ID of prediabetes, Type 1 DM, Type 2 DM, hypertension, and hyperlipidemia are shown on this page (Health-related outcomes data, https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/health-related-outcomes-data).

To broadly assess the impact of obesity and metabolic factors on the protective effect of COVID-19 vaccines against the risk of severe COVID-19-related events, we divided participants into four groups based on the presence or absence of obesity, metabolic abnormalities and vaccination, including: (1) unvaccinated participants without obesity or metabolic abnormalities, (2) unvaccinated participants with obesity or metabolic abnormalities, (3) vaccinated participants without obesity or metabolic abnormalities, and (4) vaccinated participants with obesity or metabolic abnormalities. In addition, to assess the association between obesity and metabolic abnormalities co-existing with the risk of outcome, we distinguished four metabolic obesity phenotypes based on the presence of obesity and metabolic abnormalities, including: (1) non-obese and no metabolic abnormalities; (2) non-obese and metabolic abnormalities; (3) obese and no metabolic abnormalities; and (4) obese and metabolic abnormalities. Moreover, we divided the population into another eight groups based on the presence of obesity and the number of metabolic abnormalities: (1) non-obese and with no metabolic abnormality; (2) non-obese and with one metabolic abnormality; (3) non-obese and with two metabolic abnormalities; (4) non-obese and with three metabolic abnormalities; (5) obese and with no metabolic abnormality; (6) obese and with one metabolic abnormality; (7) obese and with two metabolic abnormalities; (8) obese and with three metabolic abnormalities. Data obtained through the baseline touch screen questionnaire, genotype, hospital admission, and death register data were used to evaluate several potential confounders, including: age at the time of the COVID-19 test, sex, race (classed as nonwhite and white ethnic background), smoking status (never, previous, current), alcohol abuse/dependence, blood type extracted from imputed genotyped data, close to major road, and comorbidities (asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, interstitial lung disease, ischemic heart diseases, heart failure, liver cirrhosis, chronic kidney disease (CKD), dementia, mania, bipolar disorder, and depression, sleep disorder, osteoarthritis, and immunodeficiency). Comorbidities were identified by self-reporting, medical records and death records. ICD-10 codes were used for cause of death for all participants and to identify comorbidities.

The NHIS reported weight and height values for all participants. BMI was calculated by dividing weight in kilograms by height in meters squared. Participators were classified as obese if their BMI was greater than 30.0 kg/m^2. In addition, hypertension, hyperlipidemia, and hyperglycemia (prediabetes and diabetes) were determined directly from participants' questionnaire responses. In addition, we distinguished four and eight metabolic obesity phenotypes according to the status of obesity and metabolic abnormalities for further analysis, and the grouping method was consistent with those based on UK biobank database.

Ascertainment of intervention factors

The UK Biobank released the primary care (GP) data in July 2020 in an effort to boost COVID19-related research. This initial release of primary care data contains data for approximately 409,000 participants in England covering the GP practices with TPP (https://www.tpp-uk.com/) or EMIS (https://www.emishealth.com/) as their data system supplier. Primary health care data for Scotland and Wales were subsequently made available. The GP prescription records contain data from the GP system suppliers and contains coded prescribed medications (including prescription date, drug code and, where available, drug name and quantity). The data are coded mainly using dm+d. The GP prescription records (TPP source) covering 184,574 participants and GP prescription records (EMIS source) covering 242,349 participants.

In our study, specific drug information was obtained from DrugBank (https://go.drugbank.com/) and data regarding the use of antihypertensive drugs, glucose-lowering drugs, and lipid-lowering drugs was also obtained from primary care prescription records, including the drug brand and the date of receipt of each drug. Finally, we obtained information on a total of 27 antihypertensive drugs, 11 lipid-lowering drugs, and 23 hypoglycemic drugs from the UK Biobank (Table S9). Participants who had a history of drug treatment in the 90 days prior to a SARS-COV-2 test were considered to have recently undergone antihypertensive, glucose-lowering, or lipid-lowering therapy. The dm+d codes were used to identify these therapeutic drugs, and the relevant codes are shown in Table S9. In addition, after determining the definition of medical therapy for patients, we divided patients with hypertension, hyperglycemia, or hyperlipidemia into treated and non-treated groups based on whether they were taking medical therapy, and then assessed differences in the risk of COVID19-related serious adverse events between treated and untreated groups, respectively.

In the 2021 NHIS, participants were asked questions "Now taking high blood pressure medication?", "Now taking cholesterol medication", "Taking diabetic pills" and "Taking insulin". Based on participants' answers ("Yes" or "No") to the above questions, we were able to determine whether patients with metabolic abnormalities receive relevant medical interventions. However, due to the limitations of the survey, we were unable to obtain information on the time, type, dosage, and duration of drug use.

Ascertainment of outcomes

The outcome used in this study was severe COVID-19-related events, including COVID-19-related hospital admission and death. COVID-19-related hospital admission and death events were collected through certified hospital admission or death records with ICD-10 codes (U071, U072, and B972), respectively.

In the 2021 NHIS, severe COVID-19-related events were defined as severe COVID-19 symptoms rather than the risk of COVID-19-related hospitalizations or deaths. Participants were asked questions "How would you describe your coronavirus symptoms when they were at their worst? Would you say no symptoms, mild symptoms, moderate symptoms, or severe symptoms?". Based on participants' answers to the above questions (no, mild, moderate, severe symptoms), outcomes were divided into two groups: those with severe symptoms and those without severe symptoms.

QUANTIFICATION AND STATISTICAL ANALYSIS

Baseline characteristics of participants were reported for demographic and clinical characteristics of interest using counts and percentages. We applied a milestone approach[13] to deal with time-dependent dose variables, as some participants contributed follow-up time after both the first dose and the second dose. For participants with only one dose, we followed them until they had the event of interest, including hospital admission, death, or reaching the study end. For those with two or more doses of vaccine, we divided the follow-up period into two phases. The first phase covered the period from 14 days after the first vaccination to 14 days after the second vaccination, indicating that outcomes within 14 days after the second dose were attributed to the first dose. The second phase included the time period from 14 days after the second dose until they had the event of interest or reached the study end (Figure S1C).

In order to identify modifiable risk factors other than age, sex, race, and severe comorbidities, we first compared the number and proportion of multiple factors in vaccinated and unvaccinated patients who experienced severe COVID-19-related clinical events. Next, a multivariable Cox proportional hazards regression model was used to assess the association between exposure factors and severe COVID-19-related events with potential confounding. The target variable (severe COVID-19-related event) is binary and takes only two values, 0 or 1. For some participants, COVID-19-related hospitalizations and deaths may have occurred consecutively, while for some patients only COVID-19-related hospitalizations or deaths may have occurred. To make more efficient use of time-event data, we used death-related follow-up times in COX regression models for patients who had consecutive COVID-19-related hospitalizations and deaths. The multivariate Cox proportional hazards regression models were adjusted for age, sex, race, smoking status, alcohol abuse/dependence, vaccine dose, position (close to the main road), obesity, hypertension, hyperglycemia, and hyperlipidemia. The main study was to assess the association between exposure factors, in particular obesity and metabolic abnormalities, and the risk of COVID-19-related severe clinical events (i.e., hospitalization and death due to COVID-19) 14 days or more after the first dose of vaccine overall. An adjusted odds ratio (aHR) higher than 1.0 for this model indicated participants with risk factors, such as obesity and metabolic abnormalities, were more likely to experience severe COVID-19-related events than those without risk factors. In stratified secondary analyses, the Cox proportional hazards regression was used to assess HRs for the COVID-19-related hospitalization and mortality, respectively. For the secondary outcome, we fitted one model for COVID-19-related hospital admission and another model for COVID-19-related mortality.

In this study, we primarily wanted to assess the moderating effect of obesity and metabolic abnormalities on the relationship between multiple risk factors and severe COVID-19-related events. Moderation analysis allows us to test for the influence of a third variable, such as obesity and metabolic abnormalities, on the relationship between multiple risk factors and severe COVID-19-related events, such as ischemic heart disease and severe COVID-19. Rather than testing a causal link between these other variables, moderation tests for under what conditions an effect occurs. Moderators may strengthen, weaken, or reverse the nature of a relationship. Since risk factors, potential moderators, and outcome factors were categorical variables, multi-way analysis of variance was used to analyze the moderating effects.[30] To assess the extent to which obesity and metabolic abnormalities moderate the common risk factors for severe COVID-19,[31] we first estimated the effect of risk factors on the severe clinical events with adjustment for confounders, including age, sex, race, smoking status, and alcohol abuse/dependence). Then, we added a combination of three metabolic abnormalities with and without obesity as moderators to the model. To assess the extent to which obesity and metabolic abnormalities moderate the common risk factors, such as ischemic heart disease, for severe COVID-19 related events. We estimated the percentage of excess risk modulated (PERM) with the HRs[31] as:

$$\mathrm{PERM} = \frac{\mathrm{HR(confounders\ adjusted)} - \mathrm{HR(mediator\ adjusted)}}{\mathrm{HR(confounders\ adjusted)} - 1} \times 100$$

In addition, to evaluate the association of obesity or various metabolic abnormalities alone with the risk of severe COVID-19 events in unvaccinated and vaccinated populations, we selected participants without the obesity and metabolic abnormalities as a control group, and then selected only patients with obesity but without metabolic abnormalities as an isolated obesity group. The isolated hypertension group consisted of patients with hypertension but no obesity or other metabolic abnormalities, the isolated hyperglycemia group included patients with hyperglycemia but no obesity or other metabolic abnormalities, and the isolated hyperlipidemia group consisted of patients with hyperlipidemia but no obesity or other metabolic abnormalities. Then multivariate Cox proportional hazards regression models were used to evaluate the association between simple obesity, simple hypertension, simple hyperglycemia, and simple hyperlipidemia and the risk of severe COVID-19-related events in vaccinated and unvaccinated participants. The multivariate Cox proportional hazards regression models were adjusted for age, sex, race, smoking status, and alcohol abuse/dependence.

To further clarify the association between pharmacological interventions for metabolic abnormalities and the risk of severe COVID-19, we evaluated the impact of antihypertensive, glucose-lowering, and lipid-lowering drug treatments on the risk of severe

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COVID-19 in patients with hyperglycemia, hypertension and hyperlipidemia, respectively. As mentioned in the methods section, we divided patients with hypertension, hyperglycemia, or hyperlipidemia into treated and non-treated groups based on whether they were taking medical therapy, then multivariate Cox proportional hazards regression models were then used to compare the differences in the risk of severe COVID-19-related events between treated and untreated patients with metabolic abnormalities compared with those without metabolic abnormalities. In a sensitivity analysis, these models were repeated with participants stratified by vaccination status (vaccination or not) and dose (one dose, two doses or more). The multivariate Cox proportional hazards regression models were adjusted for age, sex, race, smoking status, alcohol abuse/dependence, obesity, blood pressure lowering therapy, glucose lowering therapy, lipid lowering therapy, ischemic heart disease, and heart failure. Kaplan-Meier survival curves and Nelson-Aalen cumulative hazard functions were plotted according to the above groups for visualization, it is important to note that severe COVID-19-related events began with the diagnosis of SARS-COV2 infection and not with vaccination. In addition, in assessing the impact of glucose-lowering drug treatments on the risk of severe COVID-19 in patients with hyperglycemia, we excluded patients with type 1 diabetes and those using insulin. Type 1 diabetes occurs when the pancreas stops making insulin. Clinically, patients with type 1 diabetes need regular insulin treatment, and some patients with type 2 diabetes who cannot control their blood glucose level with glucose-lowering drugs also need regular insulin treatment. Once the insulin treatment is stopped, patients will have serious clinical symptoms, even life-threatening. Therefore, insulin therapy is necessary for those patients who have failed to respond to glucose-lowering drugs, regardless of whether they have received COVID-19 vaccine. However, for many people with type 2 diabetes, glucose-lowering drugs can effectively control blood glucose levels, but many of them do not actively and appropriately receive glucose-lowering drugs. Therefore, for this subset of patients with type 2 diabetes, it is critical to evaluate the impact of glucose-lowering therapy on the risk of severe COVID-19-related events, so as to propose the protective effect of active glucose-lowering treatment on the risk of severe COVID-19-related events in patients with diabetes. Thus, we excluded patients with type 1 diabetes and those receiving insulin therapy, and focused on evaluating the protective effect of glucose-lowering drugs on the risk of severe COVID-19-related events in patients with type 2 diabetes.

In the cross-section study based on data from 2021NHIS, we aim to assess the association of metabolic obesity phenotypes with severe COVID-19 symptoms in vaccinated and unvaccinated populations. Logistic regression models were used to analyze the association between exposure and severe COVID-19 symptoms, adjusting for covariates age, sex, smoking status, vaccine dose, comorbidities (COPD, ischemic heart disease, liver cirrhosis, CKD, osteoarthritis, asthma, dementia, mania bipolar disorder depression, and immunodeficiency). Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 16.0 (Stata Corp., College Station, Texas, USA). Statistical significance was indicated by 95% confidence intervals (CIs) not containing the null or a two tailed test with $p < 0.05$.