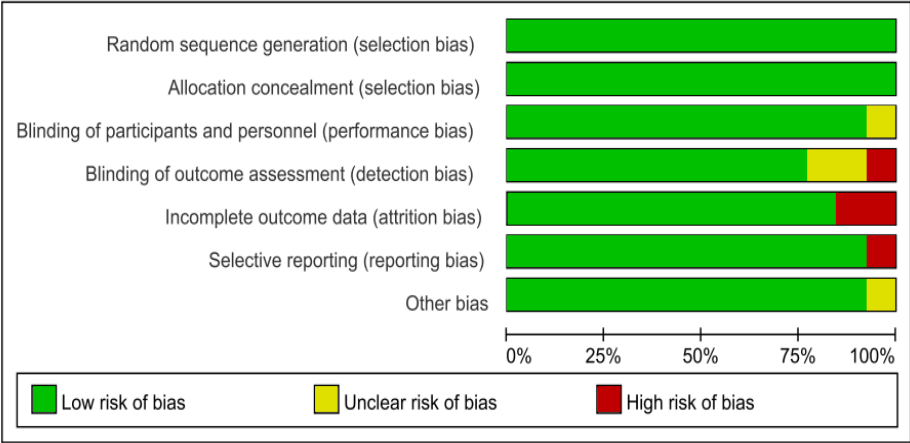
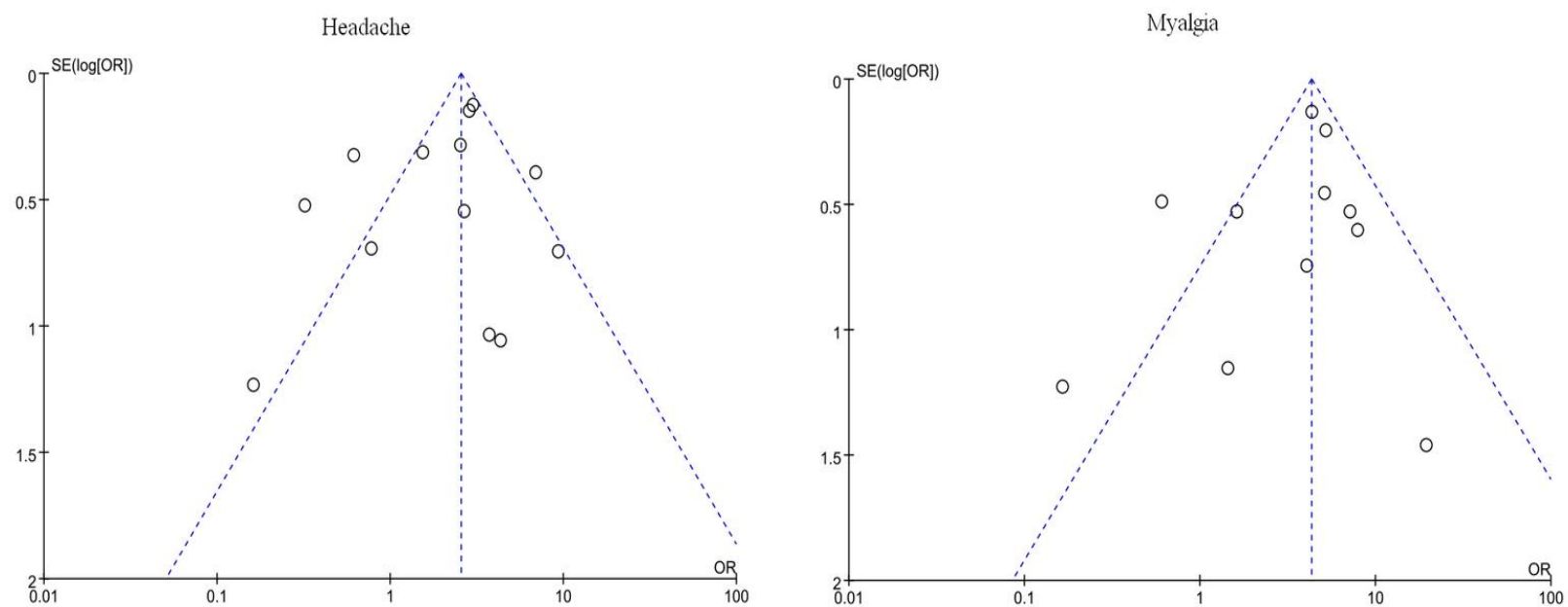


Supplementary Materials



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chappell 2021	+	+	+	-	+	+	+
Chu 2021	+	+	+	?	+	+	+
Folegatti 2020	+	+	+	+	+	+	+
Keech 2020	+	+	?	+	+	+	+
Mulligan 2020	+	+	+	+	+	+	+
Raches 2021 & 2021(2)	+	+	+	+	-	+	+
Richmond 2021	+	+	+	+	+	+	?
Walsh, 2020	+	+	+	+	+	+	+
Wu & Zhang 2021	+	+	+	+	+	+	+
Xia 2020	+	+	+	+	-	+	+
Xia 2020(2)	+	+	+	?	+	-	+
Yang 2021	+	+	+	+	+	+	+
Zhu 2020(2)	+	+	+	+	+	+	+

Figure S1. Risk of bias graph and risk of bias summary of the included studies.



	Headache	Myalgia
Begg-Mazumdar rank correlation, $Pr > z $	0.583	0.640
Egger's Test, $P > t $	0.283	0.311

Figure S2. Funnel diagram, Begg-Mazumdar rank correlation and Egger's bias test of publication bias of headache and myalgia

Table S1. Nervous and muscular adverse events in phase 1/2 randomized, blinded, and controlled clinical trial after COVID-19 vaccination

Author/ year of published	Events	No. of events/total (%)	
		Vaccine	Control
Xia 2020 [1]	Headache	7/432 (1.6)	3/144 (2.1)
	Myalgia	1/432 (0.2)	2/144 (1.4)
	Drowsiness	1/432 (0.2)	0/144 (0)
	Dizziness	1/432 (0.2)	0/144 (0)
Xia 2020(2) [2]	Headache	1/240 (0.4)	2/80 (2.5)
Wu 2021 [3] and Zhang 2021 [4]	Headache	15/636 (2.4)	1/156 (0.6)
	Myalgia	15/636 (2.4)	6/156 (3.8)
	Hypoesthesia	2/636 (0.3)	2/156 (1.3)
	Dizziness	2/636 (0.3)	0/156 (0)
	Drowsiness	2/636 (0.3)	1/156 (0.6)
Raches 2021[5] and Raches 2021(2) [6]	Headache	15/1347 (1.1)	5/148 (3.4)
	Tremor	4/1347(0.3)	0/148 (0)
	Dizziness	1/1347 (0.1)	1/148 (0.7)
	Sleep disturbance	1/1347 (0.1)	0/148 (0)
	Giddiness	2/1347 (0.1)	0/148 (0)
	Vertigo	0/1347 (0)	0/148(0)
Folegatti 2020 [7]	Headache	365/543 (67.2)	216/534 (40.4)
	Myalgia	321/543 (59.1)	133/534 (24.9)
	Feeling abnormal	1/543 (0.2)	0/534 (0)
	Muscle spasms/ musculoskeletal stiffness	2/543 (0.4)	0/534 (0)
	Abnormal sleep-related event/ insomnia	1/543 (0.2)	1/534 (0.2)
	Dysgeusia	0/543 (0)	1/534 (0.2)
	Paraesthesia	1/543 (0.2)	0/534 (0)
	Dizziness	2/543 (0.4)	0/534 (0)
Zhu 2020 [8]	Headache	109/382 (28.5)	17/126 (13.5)
	Myalgia	62/382 (16.2)	3/126 (2.4)
	Dizziness	5/382 (1.3)	1/126 (0.8)
	Hypersensitivity	0/382 (0)	2/126 (1.6)
	Syncope	2/382 (0.5)	0/126 (0)
	Hypoaesthesia	1/382 (0.3)	0/126 (0)
	Insomnia	1/382 (0.3)	0/126 (0)
	Somnolence	2/328 (0.5)	1/126 (0.8)
Keech 2020 [9]	Headache	66 /189 (30.7)	18/70 (25.7)
	Myalgia	61 /189 (28.4)	6 /70 (8.6)
Richmond 2021 [10]	Headache	38/238 (16.0)	4 /60 (6.7)
	Myalgia	29/238 (12.2)	2 /60 (3.3)
Chappell 2021 [11]	Headache	34/163 (20.9)	21/70 (30.0)
	Myalgia	18/163 (11.0)	5 /70 (7.1)
	Paraesthesia	1/163 (0.6)	1/70 (1.4)

	Radicular pain	1/163 (0.6)	0/70 (0)
Yang 2021 [12]	Headache	9/1607 (0.6)	1/770 (0.1)
	Myalgia	3/1607 (0.2)	1/770 (0.1)
Chu 2021 [13]	Headache	301/796 (37.8)	69/393 (17.6)
	Myalgia	234/796 (29.4)	29/393 (7.4)
Walsh 2020 [14]	Headache	136/300 (45.3)	8/75 (10.7)
	Myalgia	86/300 (28.7)	4/75 (5.3)
Mulligan 2020 [15]	Headache	42/60 (70.0)	3/15 (20.0)
	Myalgia	23/60 (38.3)	0/15 (0)
		2027/6933	570/2641
		(29.2) *	(21.6) *

* compared with control, P<0.05. Except for annotation, the number were person-time.
Injection of the same person experiencing twice would be recorded as two.

Table S2. The incidences of headache and myalgia with or without prophylactic paracetamol [7]

Group		No. of events (%)	
		Headache	Myalgia
Paracetamol	Vaccine (n=56)	34 (60.7) *	27 (48.2) *
	Control (n=57)	21 (36.8)	15 (26.3)
No paracetamol	Vaccine (n=487)	331 (68.0) *	294 (60.4) *
	Control (n=477)	195 (40.9)	118 (24.7)

* compared with placebo, $P < 0.05$.

Table S3. Nervous and muscular adverse events in phase 1/2 open-label clinical trial
on COVID-19 vaccination

Study	Vaccine	Group	No. of events (%)		
			Headache	Myalgia	Other NMAEs
Logunov 2020 [16]	replication-incompetent vectors vaccine	Single rAd26 or rAd5 (n=36)	16 (44.4)	8 (22.2)	NA
		rAd26 and rAd5 (n=40)	16 (40.0)	11 (27.5)	NA
Zhu 2020(2) [17]	replication-incompetent vectors vaccine	5x10 ¹⁰ viral particles/mL (n=36)	14 (38.9)	7 (19.4)	1 (2.8) ^b
		1x10 ¹¹ viral particles/mL (n=36)	11 (30.6)	3 (8.3)	0 (0)
		5x10 ¹¹ viral particles/mL (n=36)	17 (47.2)	8 (22.2)	1 (2.8) ^b
Jackson 2020 [18] and Anderson 2020 [19]	mRNA	1 st Vaccination (n=85)	19 (22.4)	14 (17.1)	0 (0)
		2 nd Vaccination (n=82)	43 (50.6) ^a	45 (54.9) ^a	2 (2.4) ^c
Total			136/351 (38.7)	96/351 (27.4)	4/275 (1.5)

* compared with the 1st vaccination, $P < 0.05$. † dizziness. ‡ syncope and lightheadedness. NMAEs= nervous and muscular adverse events. NA= not available.

Table S4. Headache and myalgia in phase 3 clinical trial on COVID-19 vaccination*

	Inactivated vaccine			Replication-incompetent vectors vaccine				mRNA vaccine				Total	
	Kaabi 2021 [20] [†]			Voysey 2020 [21]		Logunov 2021 [22] [‡]		Baden 2020 [23] [§]					
	Vaccine		Control (alum adjuvant) n=13453	Vaccine (5x10 ¹⁰ viral particles/mL) n=12021	Control (MenACW Y vaccine) n=11724	Vaccine n=1029	Control (vaccine buffer) n=340	Vaccine		Control			
	WIV04 n=13464	HB02 n=13471						1st injection n=15168	2nd injection n=14677	1st injectio n n=15155	2nd injectio n n=14566		
Headache	1733	1761	1673	NA	NA	30	9	4951	8602	4027	3410	17077/57809	9139/43514
No. (%)	(12.9)	(13.1)	(12.4)			(2.9)	(2.6)	(32.6) [¶]	(58.6) ^{¶,}	(26.6)	(23.4)	(29.5) [¶]	(21.0)
Myalgia	722	739	730	1	0	9	3	3441	8508	2071	1809	13420/69830	4613/55238
No. (%)	(5.4)	(5.5)	(5.4)	(<0.1)	(0)	(0.9)	(0.9)	(22.7) [¶]	(58.0) ^{¶,}	(13.7)	(12.4)	(19.2) [¶]	(8.4)

* Studies contained data of phase 3, and partly contained phase 1 and/or 2. [†] Observation was seven days. And a participant was only counted once in the specific reaction category even though a participant could have more than 1 adverse reaction. [‡] Adverse events registered during the analyzed period and the subjects were over 60 years old in the vaccine/control group. [§] Solicited NMAEs within 7 days after vaccination in safety set were counted. [¶] Compared with control, P<0.05. ^{||} Compared with the 1st injection, P<0.05. NA= not available.

Table S5. Headache and myalgia subgroup in study of Baden 2020 [23] *

	mRNA vaccine							
	18~65 years old				≥65 years old			
	Vaccine		Control		Vaccine		Control	
	1st injection n=11406	2nd injection n=10985	1st injection n=11407	2nd injection n=10918	1st injection n=3762	2nd injection n=3692	1st injection n=3748	2nd injection n=3648
Headache	4030	6898	3304	2760	921	1704	723	650
No. (%)	(35.3) ^{†,§}	(62.8) ^{†,‡,§}	(29.0)	(25.3)	(24.5)	(46.2) ^{†,‡}	(19.3)	(17.8)
Myalgia	2699	6769	1628	1411	742	1739	443	398
No. (%)	(23.7) ^{†,§}	(61.6) ^{†,‡,§}	(14.3)	(12.9)	(19.7) [†]	(47.1) ^{†,‡}	(11.8)	(10.9)

* Solicited NMAEs within 7 days after vaccination in safety set were counted. [†] Compared with corresponding control, P<0.05. [‡] Compared with 1st vaccination of the same group, P<0.05. [§] Compared with older (≥65 years old), P<0.05. No.= number.

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