

S1 Table. Characteristics of included studies.

No	Study	Sample size	Treatment	Intervention duration	Comparison groups	Outcome measure of interest	Effect sizes
Human <i>in vivo</i> studies							
1	de Kruif <i>et al.</i> (2007)	Human healthy male subjects (n = 8)	Administration with LPS (4 ng/kg)	1.5h 4h 24h 3h 4h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.42 (0.29, 2.95) TNF- α protein expression: 0.00 (-0.98, 0.98) TNF- α protein expression: 0.00 (-0.98, 0.98) (Positive favours one-challenge) IL-6 protein expression: 1.21 (0.11, 2.30) (Positive favours one-challenge) IL-6 protein expression: 1.25 (0.15, 2.35)
2	De Vox <i>et al.</i> (2009)	Human healthy male subjects (n = 6)	Administration with LPS (4 ng/kg)	1.5h 4h 1h-2h (1 st), 24h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression TNF- α protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.51 (0.16, 2.86) TNF- α protein expression: 0.00 (-1.13, 1.13) (Negative favours one-challenge) TNF- α protein expression: -0.25 (-1.38, 0.89) (Negative favours one-challenge) IL-6 protein expression: -0.35 (-1.50, 0.79)
3	Draisma <i>et al.</i> (2009)	Human healthy male subjects (n = 14)	Administration with LPS (2 ng/kg)	1.5h 4h 1.5h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 4.01 (2.65, 5.36) (Positive favours one-challenge) TNF- α protein expression: 0.00 (-0.74, 0.74) (Positive favours one-challenge) IL-6 protein expression: 2.97 (1.85, 4.09)

				4h 1h (1 st), 2h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	IL-6 protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 0.88 (0.10, 1.66) (Negative favours one-challenge) TNF- α protein expression: -0.91 (-1.69, -0.12) (Negative favours one-challenge) IL-6 protein expression: -2.29 (-3.28, -1.31)
4	Grondman <i>et al.</i> (2019)	Human healthy male subjects (n = 15)	Administration with LPS (2 ng/kg) (1 st); ex vivo monocytes stimulated with LPS (10 ng/ml) (2 nd)	4h or 7d (1 st); 24h (2 nd)	Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression IL-6 protein expression	Not estimable Not estimable
5	Hoogerwerf <i>et al.</i> (2008)	Human healthy male subjects (n = 8)	Bronchial instillation of LPS (4 ng/kg)	6h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 0.70 (-0.32, 1.72)
6	Koch <i>et al.</i> (2017)	Human healthy male subjects (n = 15)	Administration with LPS (2 ng/kg)	0, 1, 1.5, 2, 3, 4, 5, 6, 7, 8h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	Not estimable
7	Kox <i>et al.</i> (2011)	Human healthy male subjects (n = 12)	Administration with LPS (4 ng/kg)	1.5h 4h 1.5h 4h 1.5h (1 st), 1.5h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two-challenges	TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression TNF- α protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.46 (0.54, 2.38) (Positive favours one-challenge) TNF- α protein expression: 2.79 (1.62, 3.97) (Positive favours one-challenge) IL-6 protein expression: 2.06 (1.03, 3.08) (Positive favours one-challenge) IL-6 protein expression: 0.73 (-0.10, 1.56) (Negative favours one-challenge)

			Administration with LPS (4 ng/kg)		Group 2: One-challenge	IL-6 protein expression	TNF- α protein expression: -0.94 (-1.79, -0.09) (Negative favours one-challenge) IL-6 protein expression: -1.18 (-2.06, -0.30)
8	Lankelma <i>et al.</i> (2017)	Human healthy male subjects (n = 8)	Administration with LPS (4 ng/kg)	1.5h 4h 2h 4h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 0.70 (-0.32, 1.72) TNF- α protein expression: 0.00 (-0.98, 0.98) (Positive favours one-challenge) IL-6 protein expression: 0.90 (-0.14, 1.95) (Positive favours one-challenge) IL-6 protein expression: 0.77 (-0.25, 1.80)
9	Leentjens <i>et al.</i> (2012)	Human healthy male subjects (n = 6)	Administration with LPS (2 ng/kg)	0, 2, 4, 6, 8, 24h 0, 2, 4, 6, 8, 24h (1 st); 0, 2, 4, 6, 8, 24h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression IL-6 protein expression TNF- α protein expression IL-6 protein expression	Not estimable Not estimable
10	Leijte <i>et al.</i> (2018)	Human healthy male subjects (n = 10)	Administration with LPS	2.5h 4h 2.5h 4h 2.5h (1 st), 3h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 5.30 (3.27, 7.33) (Positive favours one-challenge) TNF- α protein expression: 2.96 (1.62, 4.31) (Positive favours one-challenge) IL-6 protein expression: 1.86 (0.83, 2.90) (Positive favours one-challenge) IL-6 protein expression: 1.40 (0.40, 2.41) (Negative favours one-challenge) TNF- α protein expression: -1.24 (-2.21, -0.26) (Negative favours one-challenge)

[illegible]

1	Aboyoussef <i>et al.</i> (2021)	Adult male albino rats (n = 10)	Cecal ligation and puncture (CLP)	24h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 9.43 (6.05, 12.81) (Positive favours one-challenge) IL-6 protein expression: 10.98 (7.08, 14.88)
2	Berglund <i>et al.</i> (2010)	C57BL/6 mice (n = 5-10)	3% DSS dissolved in tap water for a period of 5d followed by 2d of regular drinking water	7d	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF- α and IL-6 mRNA and protein expression	Not estimable
3	Deng <i>et al.</i> (2006)	C57BL/6J mice (n = 5)	Cecal ligation and puncture (CLP) Inoculation with <i>P. aeruginosa</i> CLP (1 st); lung macrophages extracted and <i>ex vivo</i> challenged with LPS (1 μ g/ml) (2 nd) CLP (1 st), macrophages extracted and <i>ex vivo</i> challenged with LPS (100 ng/ml) (2 nd) CLP (1 st), inoculation with	24h 24h 6h 24h (1 st), 6h (2 nd) 24h (1 st), 16h (2 nd) 24h (1 st), 6h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge Group 1: Two-challenges Group 2: One-challenge Group 1: IRAK3 knockout	IRAK3 mRNA expression TNF- α protein expression TNF- α protein expression IRAK3 mRNA expression TNF- α protein expression TNF- α mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 15.59 (4.78, 26.40) (Positive favours one-challenge) TNF- α protein expression: 2.19 (0.44, 3.93) (Positive favours one-challenge) TNF- α protein expression: 1.70 (0.14, 3.27) (Positive favours two-challenge) IRAK3 mRNA expression: 1.14 (-0.45, 2.73) (Negative favours one-challenge) TNF- α protein expression: -1.05 (-2.42, 0.32) (Positive favours IRAK3 knockout)

			<i>P. aeruginosa</i> (2 nd) CLP (1 st), inoculation with <i>P. aeruginosa</i> (2 nd)	24h (1 st), 24h (2 nd)	Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF- α protein expression	TNF- α mRNA expression: 1.39 (-0.29, 3.07) (Positive favours IRAK3 knockout) TNF- α protein expression: 1.49 (0.00, 2.99)
4	Funahashi <i>et al.</i> (2019)	C57BL/6 mice (n = 6-7)	CLP	6h 24h 6h 24h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 0.72 (-0.47, 1.90) (Positive favours one-challenge) TNF- α protein expression: 0.56 (-0.56, 1.68) (Positive favours one-challenge) IL-6 protein expression: 2.34 (0.73, 3.95) (Positive favours one-challenge) IL-6 protein expression: 32.07 (18.02, 46.12)
5	Gandhirajan <i>et al.</i> (2021)	C57BL/6 mice (n = 5)	Intraperitoneally injected 250 μ l cecal slurry (CS)-induced sepsis	4h, 24h	Group 1: One-challenge Group 2: Control	TNF- α and IL-6 protein expression	Not estimable
6	Gong <i>et al.</i> (2017)	C57BL/6 mice (n = 8)	Inhalation with LPS (100 μ g/mL) for 30min	24h (outcomes measured after challenge)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF- α protein expression IL-6 protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.75 (0.55, 2.95) (Positive favours one-challenge) IL-6 protein expression: 6.37 (3.40, 9.35) (Positive favours IRAK3 knockout) TNF- α protein expression: 0.24 (-0.74, 1.23) (Negative favours IRAK3 wildtype)

			Cigarette smoking exposure (1 st), inhalation with LPS (100 µg/mL) for 30min (2 nd)	3d (1 st), 24h (2 nd)	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF- α protein expression IL-6 protein expression	IL-6 protein expression: -0.93 (-2.05, 0.19) Not estimable.
7	Gribar <i>et al.</i> (2009)	C57BL/6 mice (n = 4)	Injected with LPS (5 mg/kg)	3h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	(Positive favours one-challenge) IL-6 protein expression: 4.54 (1.12, 7.96)
8	Han <i>et al.</i> (2008)	BALB/c mice (n = 2)	Injection with 45 mg/kg LPS Injection with 15 mg/kg LPS or 300 mg/kg pLTA (1 st), injection with 45 mg/kg LPS (2 nd)	24h 24h (1 st), 24h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression TNF- α protein expression	(Positive favours one-challenge) TNF- α protein expression: 4.78 (-22.33, 31.89) (Negative favours one-challenge) TNF- α protein expression: -3.43 (-22.96, 16.09)
9	Hayashi <i>et al.</i> (2009)	C57BL/6 mice (n = 8-10)	Injection with LPS (2 µg per mouse) Injection with LPS (2 µg per mouse) Injection with 1V136, Pam3CSK4 or pIC Injection with 1V136 (1 st), mice injected with 1V136, Pam3CSK4, pIC, LPS or ISS-ODN (2 nd)	2h 2h 2-3h 3d (1 st), 2h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	TNF- α protein expression IL-6 protein expression TNF- α and IL-6 protein expression TNF- α and IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.60 (0.51, 2.70) (Positive favours one-challenge) IL-6 protein expression: 3.98 (2.24, 5.72) Not estimable Not estimable

10	Hoogerwerf <i>et al.</i> (2012)	C57BL/6 (n = 8)	Infection with 1×10^4 CFU of <i>K. pneumoniae</i>	24h 3h 3h 24h 24h	Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression TNF- α protein expression IL-6 protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) IRAK3 mRNA expression: 2.84 (1.34, 4.34) (Positive favours IRAK3 knockout) TNF- α protein expression: 0.46 (-0.54, 1.45) (Positive favours IRAK3 knockout) IL-6 protein expression: 0.57 (-0.43, 1.58) (Negative favours IRAK3 wildtype) TNF- α protein expression: -0.65 (-0.54, 1.45) (Negative favours IRAK3 wildtype) IL-6 protein expression: -1.68 (-2.86, -0.49)
11	Kallapur <i>et al.</i> (2007)	Sheep (n = 5 – 9/ group)	Injection with LPS (10 mg) twice (1 st), lung or blood monocytes extracted and in vitro stimulated with LPS (100 ng/mL) (2 nd)	2d and 7d (1 st) 16h (2 nd)	Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression	Not estimable
12	Kim <i>et al.</i> (2008)	BALB/c mice (n = 3)	Injection with 10 – 40 μ g/mouse CpGDNA Injection with 10 – 40 μ g/mouse	24h 24h (1 st), 6h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression TNF- α and IL-6 protein expression	Not estimable Not estimable

			CpGDNA (1 st), CpGDNA (2 nd)				
13	Kingsley <i>et al.</i> (2020)	Rats (n = 6)	Inoculation with 600 CFU of <i>E. coli</i> .	12h	Group 1: One-challenge Group 2: Control	TNF- α and IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 3.95 (1.71, 6.78) (Positive favours one-challenge) IL-6 protein expression: 12.22 (6.15, 18.29)
14	Krogmann <i>et al.</i> (2020)	C57BL/6J mice (n = 2-4)	Injected mice with 20-100 μ g R848 (TLR7 ligand)	2h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	Not estimable
15	Li <i>et al.</i> (2013)	BALB/c mice (n = 3-6)	Injection with LPS (0.2 mg/kg) (1 st), injection with LPS (10 mg/kg) (2 nd)	24h (1 st), 3h (2 nd)	Group 1: Two-challenges Group 2: One-challenge	IRAK3 protein expression (n = 3) TNF- α protein expression (n = 6)	(Positive favours two-challenge) IRAK3 protein expression: 5.71 (-0.03, 11.45) (Negative favours one-challenge) TNF- α protein expression: -11.99 (-17.95, -6.03)
16	Li <i>et al.</i> (2016)	Pig (n = 3)	Oral administration with <i>E. coli</i> (1×10^9 CFU/kg). Diet supplemented with <i>L. acidophilus</i> (1 st), oral administration with <i>E. coli</i> (1×10^9 CFU/kg)	3h 14d (1 st), 3h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	IRAK3 mRNA expression TNF- α protein expression IRAK3 mRNA expression TNF- α protein expression	Not estimable Not estimable
17	Lyn-Kew <i>et al.</i> (2010)	C57BL/6J mice (n = 5)	CLP	24h 24h	Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout	IRAK3 mRNA expression TNF- α mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 4.29 (-0.15, 8.72) (Positive favours IRAK3 knockout)

			CLP (1 st); pulmonary macrophages extracted and stimulated 1 mg/ml LPS (n = 3)	24h (1 st), 4h (2 nd)	Group 2: IRAK3 wildtype Group 1: Two- challenges Group 2: One-challenge Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression TNF- α mRNA expression	TNF- α mRNA expression: 1.16 (- 0.24, 2.57) (Positive favours two-challenges) IRAK3 mRNA expression: 4.06 (- 0.17, 8.29) (Positive favours IRAK3 knockout) TNF- α mRNA expression: 1.81 (0.20, 3.41)
18	Miyata <i>et al.</i> (2015)	C57BL/6J mice	Inoculation with 1x10 ⁷ to 5x10 ⁸ CFU of <i>Haemophilus influenzae</i>	24h	Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression TNF- α mRNA expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) IRAK3 mRNA expression: 9.61 (0.19, 19.03) (Positive favours IRAK3 knockout) TNF- α mRNA expression: 1.84 (- 0.55, 4.23) (Positive favours IRAK3 knockout) TNF- α protein expression: 1.74 (0.62, 2.87) (Positive favours IRAK3 knockout) IL-6 protein expression: 1.73 (0.60, 2.85)
19	Paik <i>et al.</i> (2019)	C57BL/6 mice (n = 3)	Administration with LPS (30 mg/kg)	18h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 16.86 (0.50, 33.22) (Positive favours one-challenge) IL-6 protein expression: 6.35 (0.01, 12.69)
20	Petzl <i>et al.</i> (2012)	Cow	Inoculation with <i>E. coli.</i>	24h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	Not estimable

			Inoculation with LPS (1 st), inoculation with <i>E. coli</i> (2 nd).	72h or 240h (1 st), 24h (2 nd)	Group 1: Two-challenges Group 2: One-challenge	IRAK3 mRNA expression	Not estimable
21	Rothschild <i>et al.</i> (2017)	Mice (n = 3-4)	3-5% DSS dissolved in tap water for a period of 5d followed by 2d of regular drinking water	7d	Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	Not estimable
22	Shao <i>et al.</i> (2011)	C57BL/6 mice (n = 3)	Injection with LPS (0.1-0.5 µg/g)	1h 6h 24h 1h 6h 24h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF-α protein expression TNF-α protein expression TNF-α protein expression TNF-α protein expression TNF-α protein expression TNF-α protein expression	(Positive favours one-challenge) TNF-α protein expression: 2.43 (-0.41, 5.27) TNF-α protein expression: 0.00 (-0.16, 0.16) (Negative favours control) TNF-α protein expression: -0.35 (-1.99, 1.28) (Positive favours one-challenge) TNF-α protein expression: 9.10 (0.17, 18.03) (Positive favours one-challenge) TNF-α protein expression: 1.14 (-0.80, 3.08) TNF-α protein expression: 0.00 (-1.60, 1.60)
23	Szatanik <i>et al.</i> (2011)	BALB/c mice (n = 6)	Injection with 5x10 ⁶ CFU of <i>N. meningitides</i>	2h, 6h, 24h	Group 1: One-challenge group Group 2: lack of control	TNF-α and IL-6 protein expression	Not estimable
24	Takebayashi <i>et al.</i> (2009)	IQI/Jic mice (n = 6)	Intraperitoneal administration with 0.3 – 0.4 mg LPS	2h - 3h	Group 1: One-challenge Group 2: Control	IRAK3 mRNA expression	Not estimable
25	Tan <i>et al.</i> (2019)	Wistar rats	Injection with LPS (0.4 mg/rat)	4h	Group 1: One-challenge Group 2: Control	TNF-α protein expression	(Positive favours one-challenge)

				16h			TNF- α protein expression: 8.22 (6.67, 9.77) (Positive favours one-challenge) TNF- α protein expression: 11.33 (9.24, 13.41)
26	Tseng <i>et al.</i> (2020)	Sprague-Dawley rats (n = 6)	Injection with LPS (10 mg/kg)	24h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 3.81 (1.64, 5.99) (Positive favours one-challenge) IL-6 protein expression: 5.75 (2.73, 8.78)
27	van der Windt <i>et al.</i> (2012)	C57BL/6 mice (n = 8)	Inoculation with 5×10^4 CFUs of <i>S. pneumoniae</i>	3h 24h 3h 24h 3h 24h 3h 24h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression TNF- α protein expression TNF- α protein expression TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 1.17 (0.08, 2.25) (Positive favours one-challenge) TNF- α protein expression: 1.42 (0.29, 2.55) (Positive favours one-challenge) IL-6 protein expression: 3.60 (1.86, 5.35) (Positive favours one-challenge) IL-6 protein expression: 1.22 (0.13, 2.32) (Positive favours IRAK3 knockout) TNF- α protein expression: 0.13 (-0.85, 1.11) (Positive favours IRAK3 knockout) TNF- α protein expression: 0.88 (-0.90, 1.06) (Positive favours IRAK3 knockout) IL-6 protein expression: 0.13 (-0.85, 1.11)

					Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IL-6 protein expression	(Negative favours IRAK3 wildtype) IL-6 protein expression: -0.09 (-1.07, 0.89)
28	Xia <i>et al.</i> (2018)	C57BL/6 mice (n = 6)	CLP (1 st), injection with LPS (10 mg/kg) (2 nd)	3d (1 st), 24h (2 nd)	Group 1: Two-challenges Group 2: One-challenge Group 1: IRAK3 knockout Group 2: IRAK3 wildtype	IRAK3 mRNA expression TNF- α protein expression TNF- α protein expression	(Positive favours two-challenge) IRAK3 mRNA expression: 4.91 (2.26, 7.56) (Negative favours one-challenge) TNF- α protein expression: -2.84 (-4.63, 1.05) (Positive favours IRAK3 knockout) TNF- α protein expression: 2.33 (0.73, 3.94)
29	Xie <i>et al.</i> (2019)	C57BL/6 mice (n = 10)	Injection with LPS (40 μ g/kg)	24h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 14.61 (9.48, 19.74) (Positive favours one-challenge) IL-6 protein expression: 8.02 (5.11, 10.92)
30	Xiong <i>et al.</i> (2011)	C57BL/6J mice (n = 3)	Inoculation with LPS (25 μ g/ mouse) Inoculation with LPS (25 μ g/ mouse), macrophages extracted and treated with 100 ng/ml LPS	24h 24h (1 st), 3 h (2 nd)	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	IRAK3 mRNA expression TNF- α mRNA expression	(Positive favours one-challenge) IRAK3 mRNA expression: 6.36 (0.01, 12.71) Not estimable
31	Yang and Zhao (2021)	Rats (n = 12)	Injection with LPS (3mg/kg)	48h	Group 1: One-challenge Group 2: Control	TNF- α and IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 3.78 (2.36, 5.20) (Positive favours one-challenge)

							IL-6 protein expression: 3.31 (2.01, 4.61)
32	Yee and Hameman (2013)	C57BL/6 mice	Injection with LPS (1 mg/kg)	2h 4h 2h 4h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression TNF- α protein expression IL-6 protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 16.50 (11.06, 21.95) (Positive favours one-challenge) TNF- α protein expression: 8.02 (5.27, 10.76) (Positive favours one-challenge) IL-6 protein expression: 1.93 (0.88, 2.97) (Positive favours one-challenge) IL-6 protein expression: 3.45 (2.05, 4.85)
33	Yu <i>et al.</i> (2017)	Wistar rats	Injection with LPS (200 μ g per mouse) Daily injection with LPS (0.1 mg/kg LPS) (1 st), on day 6 injection with LPS (200 μ g per mouse)	24h 5d (1 st), 24h (2 nd).	Group 1: One-challenge Group 2: Control Group 1: Two-challenges Group 2: One-challenge	IRAK3 mRNA expression IRAK3 protein expression	(Positive favours one-challenge) IRAK3 mRNA expression: 4.78 (2.91, 6.66) (Positive favours two-challenge) IRAK3 protein expression: 3.03 (1.67, 4.40)
34	Zhang <i>et al.</i> (2020)	C57BL/6 mice (n = 6)	CLP	24h	Group 1: One-challenge Group 2: Control	TNF- α protein expression	(Positive favours one-challenge) TNF- α protein expression: 4.28 (1.91, 6.66)
35	Zhang and Wang (2021)	Male Sprague-Dawley rats (n = 6)	5.5% (w/v) dextran sodium sulfate-treated rats	7d	Group 1: One-challenge Group 2: Control	TNF- α and IL-6 protein expression	Not estimable
36	Zhao <i>et al.</i> (2019)	BALB/c mice (n = 11)	Injection with LPS (10mg/kg)	2h 6h	Group 1: One-challenge Group 2: Control Group 1: One-challenge Group 2: Control	TNF- α protein expression TNF- α protein expression	(Positive favours one-challenge) TNF- α protein expression: 2.36 (1.22, 3.50) (Positive favours one-challenge)

				2h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	TNF- α protein expression: 2.45 (1.29, 3.60) (Positive favours one-challenge)
				6h	Group 1: One-challenge Group 2: Control	IL-6 protein expression	IL-6 protein expression: 3.24 (1.89, 4.59) (Positive favours one-challenge) IL-6 protein expression: 3.66 (2.21, 5.12)
37	Zhao <i>et al.</i> (2021)	BALB/c mice (n = 10)	Injection with LPS (2mg/kg)	24h	Group 1: One-challenge Group 2: Control	TNF- α protein expression IL-6 protein expression	(Positive favours one-challenge) TNF- α protein expression: 48.09 (31.44, 64.75) (Positive favours one-challenge) IL-6 protein expression: 48.50 (31.71, 65.30)