Supplementary material

The nephroprotective properties of extracellular vesicles in experimental models of chronic kidney disease: a systematic review.

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Supplementary Table 1. Appraisal of research methods and risk of bias summary

Study	Concentration	Size	TEM	Protein mrkers	IF	Blinding	Ethics statement	Randomisation	COI
Cambier, 2018 [17]	MF, concentration	Yes (NTA)*	Yes*	Yes*	Yes	-	Yes	-	#
Cantaluppi, 2015 [18]	UC	Yes (NTA)	Yes	Yes	Yes	-	Yes	-	None
Chen, 2019 [11]	UC	Yes (DLS)	Yes	Yes	Yes	-	Yes	Yes	None
Choi, 2015 [19]	UC	-	?	-	Yes	Yes	Yes	Yes	None
Duan, 2020 [20]	UC, MF	Yes (DLS)	Yes	Yes	Yes	-	Yes	-	None
Duan, 2019 [21]	Precipitation	Yes (TEM)	Yes	Yes	Yes	-	Yes	Yes	None
Ebrahim, 2018 [22]	UC	Yes (TEM)	Yes	Yes	Yes	-	Yes	Yes	None
Eirin, 2020 [23]	UC	Yes (NTA)*	Yes*	Yes	Yes	Yes	Yes	-	#
Eirin, 2017 [24]	UC	Yes (NTA)	Yes	Yes	Yes	-	Yes	Yes	None
Grange, 2019 [25]	UC, MF	Yes (NTA)	-	MSC-EV markers only	Yes	-	Yes	Yes	#
He, 2012 [26]	UC	Yes (TEM)	Yes	-	Yes	Yes	Yes	Yes	-
He, 2015 [27]	UC	Yes (TEM)	Yes*	-	Yes	Yes	Yes	Yes	None
Ji, 2020 [28]	UC, MF	Yes (NTA)	Yes	Yes	Yes	-	Yes	-	None
Jiang, 2016 [29]	UC, MF, DG	Yes (TRPS)	Yes	Yes	Yes	Yes	Yes	Yes	None
Jin, 2019 [30]	Immun-P, UF	Yes (NTA)	Yes	Yes	Yes	-	Yes	-	None
Jin, 2020 [31]	Immun-P	Yes (TEM)	Yes	Yes	Yes	-	n.a.	-	None
Kholia, 2018 [32]	DG-UC	Yes (NTA)	Yes	Yes	Yes	Yes	Yes	-	-
Kholia, 2020 [33]	UC, MF	Yes (NTA)	Yes	Yes	Yes	-	Yes	-	None
Lindoso, 2020 [34]	UC	Yes (NTA)	Yes	Yes	Yes	Yes	Yes	Yes	None
Nagaishi, 2016 [35]	UC	Yes (TEM)	Yes	Yes	Yes	-	Yes	-	None
Ramirez-Bajo, 2020 [13]	UC, MF	Yes (NTA)	Yes	Yes	Yes	-	Yes	Yes	#
Sedryakyan, 2017 [36]	UC	Yes (NTA)	-	Yes	Yes	Yes	Yes	-	None
Shi, 2020 [37]	UC	Yes (NTA)	Yes	Yes	Yes	-	Yes	Yes	None
Song, 2020 [15]	UC	Yes (NTA)*	Yes*	Yes	Yes	-	Yes	-	#
Van Koppen, 2012 [12]	DG -UC	-	-	-	Yes	-	Yes	-	#
Wang, 2020 [38]	Column method	-	-	MSC-EV markers only	Yes	-	Yes	Yes	None
Wang, 2015 [39]	UC	-	-	MSC-EV markers only	Yes	Yes	Yes	Yes	None
Wang, 2016 [40]	Precipitation	?	?	?	Yes	-	Yes	-	None
Wang, 2019 [41]	UC, MF	Yes (NTA)	-	Yes	Yes	Yes	Yes	-	None
Yang, 2019 [42]	UC	Yes (TEM)	Yes	-	Yes	Yes	Yes	-	None
Zhang, 2019 [43]	Serial centrifugation	Yes (TEM)	-	Yes	Yes	-	Yes*	-	None
Zhang, 2019 [44]	UC	Yes (TEM)	-	MSC-EV markers only	Yes	-	Yes	Yes	None
Zhao, 2020 [45]	UC	Yes (NTA)	Yes	Yes	Yes	Yes	Yes	Yes	#
Zhong, 2019 [46]	UC	Yes (NTA)	Yes	MSC-EV markers only	Yes	-	Yes	Yes	None
Zou, 2018 [47]	UC	Yes (NTA)	Yes	Yes	Yes	-	Yes	Yes	None

Abbreviations: NTA – Nanoparticle tracking analysis, UC – Ultracentrifugation, TEM – Transmission Electron Microscopy, TRPS-Tunable Resistive Pulse Sensing, MF – Microfiltration, asterisk indicates that the data had been reported in the previous references by the same authors, minus indicates that information not available, n.a. indicates ethic statement was likely not required (in vitro study), # indicates that conflict of interest (COI) is reported but does not affect, in our interpretation, the study results.

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- 4) Eirin, A., Zhu, X. Y., Puranik, A. S., Tang, H., McGurren, K. A., van Wijnen, A. J., et al. (2017). Mesenchymal stem cell-derived extracellular vesicles attenuate kidney inflammation. Kidney international, 92(1), 114–124.

Supplementary table 2. Details of the design of the studies that focused on genetically modified EVs/miRNA effector molecules. Characteristics of the EV intervention, disease/animal model, time-points evaluated, and main study findings are outlined.

CKD model	Study	EV/ miRNA source	Dose	Adm- route	Dose	EV size	EV markers	Species/Model	Sex	EA	End	Main findings
UUO	Wang, 2019	miR-29- Satellite cells (m)	М	IM	n.a.	87-93 nm (NTA)	TSG101	C57BL/6J mouse (UUO)	М	1w	2w	miR-29-EVs attenuated renal fibrosis and improve kidney function in UUO mice.
UUO	Zhang, 2019	EKC (h) miR-26a- EVs	S	IM	n.a.	30-500 nm (NTA)	TSG101	C57BL/6J mouse (UUO)	М	1d	2w	miR-26a-EVs improved kidney fibrosis in UUO mice.
UUO	Wang, 2016	let7c- MSCs (h)	n.a.	n.a.	-	n.a.	?	In vitro (mouse TECs, TGF-β)	n.a.	-	-	let-7c-EVs inhibited fibrosis gene expression.
DM	Jin, 2020	MSC(m)- EVs- miR-215	n.a.	n.a.	-	87-93 nm (NTA)	CD9, CD63, CD81	In vitro (mouse podocyte, glucose)	n.a.	-	-	EVs and EV-miR-215 inhibited fibrosis gene expression.

Abbreviations: Cell of EV origin: EKC; embryonic kidney cell, MSC; mesenchymal stem cell. NTA; nanoparticle tracking analysis, TSG101; Tumor Susceptibility 101. CKD model: DM; diabetes, UUO; unilateral ureteral obstruction. TEC; tubular epithelial cell, TGF-β1; transforming growth factor β.

Supplementary Table 3. Summary of the studies which evaluated the protective effect of extracellular vesicles (EVs): study reference, cell of origin of EVs, injury model, effector molecules mediating protection, and the involvement in CKD mechanism are specified. The effect of EVs is represented: red indicates a reduction, blue indicates an elevation.

					Fibrosi	5		Cell da	amage			Inflamn	nation		Stress
Study	CKD	Cell	Mediator	GS	IF	Fibrosis Markers	Cell Death	Caspa se	ACR	KIM-1 NGAL	WBC	M1 to M2	TNF, IL-6	IL-10	Oxidati ve stress
Chen, 2019	UUO	MSC	GDNF												
Choi, 2015	UUO	MSC													
He, 2015	UUO	MSC	miRNA array		8										
Ji, 2020	UUO	MSC	CK1δ, β-TRCP		8										
Shi, 2020	UUO	MSC	MFG-E8	8											
Wang, 2020	uuo	MSC	miR-294, miR-133												
Wang, 2015	UUO	MSC	miRNA array		8										
Wang, 2016	UUO	MSC	let-7c												
Wang, 2019	UUO	SC	miR-29												
Yang, 2019	UUO	EPC													
Zhang, 2019	UUO	EKC	miR-26a												
Cantaluppi, 2015	Toxic	EPC	CD55,CD59, CFH miR-126, miR-296												
Kholia, 2018	Toxic	HLSC													
Matsakura, 2019	Toxic	MSC													
Ramirez, 2020	Toxic	MSC													
Zhang, 2019	Toxic	MSC													
He, 2012	Nx	MSC			8										
Koppen, 2012	Nx	MSC													
Cambier, 2018	нт	CPC	Y4 RNA												
Eirin, 2017	нт	MSC	IL10 mRNA												
Eirin, 2020	нт	MSC	RNA-seq												
Lindoso, 2020	НТ	MSC													
Song, 2020	нт	MSC	RNA-seq												
Zhao, 2000	НТ	MSC	miR-532-5p												
Zou, 2018	НТ	STC	mito-DNAs												
Sedryakyan, 2017	Alpor t	AFSC	VEGFR1, miRNAs												
Duan, 2000	DM	MSC	miR-26a-5p	8											
Duan, 2019	DM	uSC	miR-16-5p												
Ebrahim, 2018	DM	MSC													
Grange, 2019	DM	MSC, HLSC	miRNA array												
Jiang, 2016	DM	uSC													
Jin, 2019	DM	MSC	miR-486												
Jin, 2020	DM	MSC	miR-215-5p												
Nagaishi,2016	DM	MSC		8	8										
Zhong, 2019	DM	MSC	miR-451a		8										

Abbreviations: GS; percent glomerular sclerosis, IF; percent tubulointerstitial fibrosis ACR albumin to creatinine ratio; M1 to M2 macrophage ratio, IL-10; interleukin-10, tubular markers: KIM-1; kidney injury molecule-1, NGAL; neutrophil gelatinase-associated lipocalin, WBC; White blood cell infiltrates, NGAL; Neutrophil gelatinase-associated lipocalin,WBC; white blood cell infiltrates, Cell of EV origin: AFSC; amniotic fluid stem cell, CPC; cardiac progenitor cell, EKC; embryonic kidney cell, EPC; endothelial progenitor cell, HLSC; liver stem cell, MSC; mesenchymal stem cell, SC; satellite cell, STC; STC-like cell, uSC; urine stem cell.

Supplementary figure 1; Standardized mean difference (SMD) in glomerular filtration rate (GFR). Data represent SMD calculated for treaded versus non-treated comparisons of all records, with the 95% confidence interval (95% CI). RE, random effect



Supplementary figure 2; Subgroup analyses: standardized mean difference (SMD) in (A) serum creatinine and (B) urea. Data represent SMD based on EV intervention-related and model related factors with the 95% confidence interval (95% CI). RE, random effect.

					SMD	
Subgroup	к				with 95% CI	P-value
Therapy						
Preventive	8				-1.56 [-2.28, -0.8	5] 0.000
Curative	11	←	•		-8.68 [-15.19, -2.1	7] 0.009
Test of group d	ifferences: $Q_{b}(1) = 4.54$, p = 0.03					
Dose						
Single	5				-2.21 [-3.60, -0.8	1] 0.002
Multiple	14	-		•	-6.72 [-11.77, -1.6	7] 0.009
Test of group d	ifferences: $Q_{b}(1) = 2.84$, p = 0.09					
Transplant						
Allogenic	7				-3.53 [-5.19, -1.8	7] 0.000
Xenogenic	12			•	-6.67 [-12.84, -0.5	0] 0.034
Test of group d	ifferences: $Q_{b}(1) = 0.93$, p = 0.33					
Etiology due t	o DM					
No	9				-2.24 [-3.10, -1.3	8] 0.000
Yes	10	←	•		-8.97 [-16.41, -1.5	3] 0.018
Test of group d	ifferences: $Q_{b}(1) = 3.10$, p = 0.08					
Animal specie	S					
Mouse	15			•	-6.20 [-10.86, -1.5	5] 0.009
Rat	4			•	-2.69 [-4.74, -0.6	4] 0.010
Test of group d	ifferences: $Q_{b}(1) = 1.84$, p = 0.18					
Overall					E 14 E 0 40 1 0	01 0 000
Overall					-5.14 [-8.40, -1.8	3] 0.002
neterogeneity:	$T^{*} = 51.41, I^{*} = 99.15\%, H^{*} = 117.60$					
lest of $\theta_i = \theta_j$: C	ג(18) = 172.17, p = 0.00	[4	
		-15	-10	-5	0	

A. Differences in serum creatinine due to EV treatement-related and model-related factors

			SMD	
Subgroup	Study Cohorts		with 95% CI	P-value
Therapy				
Preventive	9	_	-1.82 [-3.27, -0.37]	0.014
Curative	9		-5.00 [-8.43, -1.56]	0.004
Test of group di	ifferences: $Q_{b}(1) = 2.79$, p = 0.09			
Dose				
Multiple	15		-3 68 [-5 87 -1 48]	0.001
Single	3		-1 65 [-3 26 -0 04]	0.045
Tost of group di	$(f_{1}) = 2.13 n = 0.14$	-	-1.05 [-3.20, -0.04]	0.045
lest of group d	$\Delta_{b}(1) = 2.13, p = 0.14$			
Transplant				
Allogenic	8		-1.96 [-3.04, -0.88]	0.000
Xenogenic	10	•	-4.44 [-7.75, -1.13]	0.009
Test of group di	ifferences: $Q_{b}(1) = 1.95$, p = 0.16			
Etiology due to	o DM			
No	8		-1.97 [-3.40, -0.54]	0.007
Yes	10	•	-4.52 [-7.73, -1.32]	0.006
Test of group di	ifferences: $Q_{b}(1) = 2.03$, p = 0.15			
Animal				
Mouse	14	•	-3.42 [-5.64, -1.19]	0.003
Rat	4	•	2.99 [-6.32, 0.35]	0.079
Test of group di	fferences: $Q_{b}(1) = 0.04$, p = 0.83			
		i and		
Overall			-3.28 [-5.07, -1.48]	0.000
Heterogeneity:	$\tau^2 = 13.98$, $I^2 = 96.84\%$, $H^2 = 31.60$			
Test of $\theta_i = \theta_j$: C	Q(17) = 172.37, p = 0.00		-	
		-8 -6 -4 -2 ()	

B. Differences in serum urea due to EV-treatement and model-related facors

Supplementary figure 3; Sensitivity analysis: standardized mean difference (SMD) in (A) serum creatinine and (B) urea for all studies in animal CKD. Data represent SMD calculated for treaded versus non-treated comparisons of all records, with the 95% confidence interval (95% CI). RE, random effect.

A. The eff	ect of I	EV-bas	sed tre	eatme	nt on p	plasma creatinie for all st	udies in animal	CKD	Weight
Study cohort	Cell	Dose	Dose	A/S	Start	EV	with 95%	CI	(%)
uuo				NO	oluli				(
He 2015	MSC	S	30*	м	2d	_	-4.42 -6.48	-2.37]	3.84
He 2015	MSC	s	30*	м	2d		-2.05 [-3.38	-0.721	3.91
Wang 2015	MSC	s	30	м	1d		-4.84 [-7.24	-2 441	3.80
Wang 2015	MSC	s	30	м	1d	←	-16 96 [-24 48	-9 451	2.83
Wang 2020*	MSC	6	-30		14		- 0.16[-1.09	1 411	2.00
Wang 2020	MSC	s	-30	B	1d		- 0.50[-0.77	1 77	3.01
Wang 2020*	MSC	e	- 20		14		- 0.16[-1.00	1 411	2.01
Wang 2020	Mac	0	~30		14	-	0.16[-1.09,	5.021	0.91
Wang 2020	Mac	0	~30		IU.		- 3.07 [1.12,	5.03	3.00
Chen 2019	MSC	5	200	M#	10		-0.08[-1.12,	0.97]	3.93
Heterogeneity: T ² = 15	.17, 1* = \$	90.19%,	H° = 26	22			-1.90[-4.57,	0.77]	
Hypertension									
Lindoso 2020	MSC	м	~20	R	1w		-4.22 [-5.68,	-2.77]	3.90
Zou 2018	STC	S	30	м	2w		-1.84 [-2.85,	-0.82]	3.93
Eirin 2017	MSC	s	100	Р	156.5	-	-0.97 [-2.02,	0.07]	3.93
Zhao 2020	MSC	S	100	Р	182.9		-1.27 [-2.43,	-0.11]	3.92
Heterogeneity: $\tau^2 = 1.5$	58, l² = 82	2.13%, H	² = 5.60			•	-2.01 [-3.37,	-0.65]	
Dishetes									
Diabetes		10	100		04		1 50 1 0 50	0.011	2.00
liana 2016		12	100		04		-1.56 [-2.50,	-0.01]	3.83
Jiang 2016	usc	12	100	.н	30		-0.53 [-1.38,	0.33]	3.94
Grange 2019	HLSC	5	100	IVI#	Sw		-0.75[-1.90,	0.40]	3.92
Grange 2019	MSC	5	100	M#	5w		0.38[-0.73,	1.50]	3.92
Ebrahim 2018	MSC	54	~30	H#	9w		-4.97[-7.05,	-2.88]	3.84
Zhong 2019	MSC	4	~40	M#	2w*		-12.54 [-16.73,	-8.35]	3.52
Zhong 2019	MSC	6	~40	M#	2w*		-35.22 [-46.76,	-23.68]	2.04
Zhong 2019	MSC	8	~40	M#	2w*	_	-32.43 [-43.05,	-21.80]	2.20
Duan 2020	MSC	12	100	м	13w#		-10.23 [-14.46,	-6.01]	3.51
Jin 2019	MSC	12	n.a.	м	13w#		-1.30 [-2.23,	-0.37]	3.93
Heterogeneity: $\tau^2 = 13$	7.61, l² =	99.62%	, H ² = 2	64.07			-8.97 [-16.41,	-1.53]	
Toxic									
Kholia 2018	HLSC	3	100	M#	3d	-	-1.58 [-2.60,	-0.56]	3.93
Kholoia, 2020	MSC	3	100	M#	3d	-	-1.74 [-2.91,	-0.56]	3.92
Heterogeneity: $\tau^2 = 0.0$	$00, I^2 = 0.$	00%, H ²	= 1.00			•	-1.65 [-2.42,	-0.88]	
E/C Ny									
Ho 2012	Mec	2	20		24		2041 0.00	0.951	2.00
Heterogeneitu net er	MSC	3	30	IVI	20		-2.04 [-3.23,	-0.85]	3.92
Heterogeneity: not ap	Dicable					•	-2.04 [-3.23,	-0.85]	
Genetic (non-DM)									
Sedryakyan 2017	AFSC	S	200	м	8w	-	-3.35 [-4.84,	-1.87]	3.90
Heterogeneity: not app	plicable					•	-3.35 [-4.84,	-1.87]	
Overall							-4.00 -6.37	-1 641	
Heterogeneity: T ² - 36	74 2 - 9	8 76%	H ² = 80	79					
Test of $\theta_i = \theta_i$: Q(26) =	240.39,	p = 0.00	00						
Test of group difference	es: Q ₆ (5)	= 7.34,	p = 0.20)		· · · · · · · · · · · · · · · · · · ·			
						-15 -10 -5 0			

Line Line Line Line Wang 2015 MSC S H M 2d -2.92 $(-4.48, -1.33)$ 4. Wang 2015 MSC S 30 M 1d -4.63 $(-3.42, -0.75)$ 4. Wang 2020 MSC S 30 M 1d -4.63 $(-3.42, -0.75)$ 4. Wang 2020 MSC S -30 R 1d -4.63 $(-3.42, -0.75)$ 4. Wang 2020 MSC S -30 R 1d -4.63 $(-4.68, -1.62)$ 4. Wang 2020 MSC S -30 R 1d -0.56 $(-7.7, 1.84)$ 4. Wang 2020 MSC S -30 R 1d -0.56 $(-7.7, 1.84)$ 4. -0.56 $(-7.7, 1.84)$ 4. -0.56 $(-7.7, 1.84)$ 4. -0.56 $(-1.63, 0.62)$ 4. -0.56 $(-1.63, 0.62)$ 4. -0.56 $(-1.63, 0.62)$ 4. -0.56 $(-1.63, 0.62)$ 4. -0.56 $(-1.63, 0.62)$ 4.	Study cohort	Cell	Dose	Single Dose	A/S	Start EV		wi	SMD th 95% C	:	Weigh
He 2015 MSC S H M 2d -2.82 -4.48 -1.35 4.48 He 2015 MSC S 30 M 1d -4.93 -7.96 -4.93 -9.02 -4.93 -9.02 -4.93 -9.02 -7.91 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -4.93 -1.96 -1.96 -1.96 -1.96 -1.96 -1.96 -1.96 -1.96 -1.96 <td>000</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>(/</td>	000										(/
Heizoris MSC S H M 2d Wang 2015 MSC S 30 M 1d Wang 2020 MSC S 30 M 1d Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d Ji 2020 MSC M(3) H R ed Heterogeneity: $r^2 = 6.36, r^2 = 9.0.49$ Diabetes Diabete	He 2015	MSC	S	н	м	2d		-2.92 [-4.48.	-1.351	4.14
Wang 2015 MSC S 30 M 1d Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d J2020 MSC S 200 M# 1d J2020 MSC S 200 M# 1d J2020 MSC M(3) H R 6d Heterogeneity: $\tau^2 = 6.36$, $t^2 = 90.44\%$, $t^2 = 10.46$ Tast of $\theta_{-} = \theta_{-} Q(p) = 71.62$, $p = 0.00$ Diabetes Dian 2019 MSC M(12) 100 R 3d Grange 2019 MSC M(5) 100 M# 5w Change 2019 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Theterogeneity: $\tau^2 = 25.71$, $t^2 = 90.44\%$, $t^2 = 10.43$ Tast of $\theta_{-} = \theta_{-} Q(p) = 71.62$, $p = 0.00$ Toxic Ramirez Bajo 2020 MSC M(12) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 30 M 2d Wan Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $\tau^4 = 0.36$, $t^2 = 69.10\%$, $t^4 = 3.24$ Tast of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.56$, $p = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.57$, $\theta_{-} = 0.07$ Text of $\theta_{-} = \theta_{-} Q(2) = 3.57$, $\theta_{-} = 0.07$	He 2015	MSC	S	н	м	2d		-2.08 [-3.42.	-0.751	4.20
Wang 2015 MSC S 30 M 1d Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d Ji 2020 MSC S 200 M# 1d Ji 2020 MSC S 200 M# 1d Ji 2020 MSC M(3) H R 6d Chen 2019 MSC M(3) H R 6d Chen 2019 MSC M(12) 100 R 3d Grange 2019 HLSC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Evahim 2018 MSC M(5) 100 M# 5w Evahim 2018 MSC M(6) -30 R# 9w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(12) n.a. M 13w# Heterogeneity: $\tau^2 = 5.7, \Gamma = 9.00$ Toxic Raminez Bajo 2020 MSC M(2) 100 M 1d Raminez Bajo 2020 MSC M(2) 100 M 1d Raminez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(2) 100 M 2w Heterogeneity: $\tau^2 = 0.5, \Gamma = 69.10\%, H^2 = 3.24$ Test of $\theta = \theta; Q(2) = 3.26, p = 0.07$ Coverall Heterogeneity: $\tau^2 = 0.56, \Gamma = 69.10\%, H^2 = 3.24$ Test of $\theta = \theta; Q(1) = 32.4, p = 0.07$ Coverall Heterogeneity: $\tau^2 = 0.56, \Gamma = 69.10\%, H^2 = 3.270$ Test of $\theta = \theta; Q(1) = 32.4, p = 0.07$ Coverall Heterogeneity: $\tau^2 = 0.56, \Gamma = 69.10\%, H^2 = 3.270$ Test of $\theta = \theta; Q(1) = 32.4, p = 0.07$ Coverall Heterogeneity: $\tau^2 = 0.56, \Gamma = 69.10\%, H^2 = 3.270$ Test of $\theta = \theta; Q(1) = 32.4, p = 0.07$ Coverall Heterogeneity: $\tau^2 = 1.1.51, p = 0.01$	Wang 2015	MSC	S	30	м	1d		-4.93 [-7.36.	-2.501	3.84
Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Charles 20 MSC M(3) H R 6d Heterogeneity: $t^2 = 6.38$, $t^2 = 90.44\%$, $t^2 = 10.46$ Test of $\theta_1 = \theta_1$ (Q(9) = 71.62, p = 0.00 Diabetes Duan 2019 MSC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Charles 20 MSC M(5) 100 M# 5w Charles 20 MSC M(5) 100 M# 5w Charles 20 MSC M(66) -30 R# 9w Charles 2019 MSC M(66) -30 R# 9w Charles 2019 MSC M(66) -30 R# 9w Charles 2019 MSC M(66) -40 M# 2w Charles 2019 MSC M(12) 100 M 1d Partice 2019 MSC M(12) 100 M 10 Partice 2019 MSC M(2) 100 M 10 Partice 2019 MSC M(3) 100 M# 3d Partice 2018 MSC M(3) 30 M 2d Partice 2018 MSC M(3) 30 M 2d Partice 2018 MSC M(3) 30 M 2d Partice 30, 2020 MSC M(3) 100 M# 3d Partice 30, 2020 MSC M(4) 7 R 7w Partice 30, 2031 MSC M(4) 7 R 7w Pari	Wang 2015	MSC	S	30	м	1d		-4.63 [-6.95,	-2.31]	3.89
Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d J 2020 MSC M(3) H R 6d J 2020 MSC M(3) H R 6d J 2020 MSC M(12) 100 R 3d Grange 2019 HLSC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Ebrahim 2018 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(6) -30 R# 9w Zhong 2019 MSC M(6) -40 M# 2w Change 2019 MSC M(12) 100 M 13w# Heterogeneity: $r^2 = 25.77$, $r^2 = 98.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$ Q(2) = 132.86, $p = 0.00$ Toxic Raminez Bajo 2020 MSC M(2) 100 M 1d Raminez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $r^2 = 0.36$, $f^2 = 90.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$ Q(2) = 3.56, $p = 0.00$ Toxic Heterogeneity: $r^2 = 0.36$, $f^2 = 90.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$ Q(2) = 3.56, $p = 0.00$ Toxic Heterogeneity: $r^2 = 0.36$, $f^2 = 90.0\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$ Q(2) = 3.56, $p = 0.00$ Toxic Heterogeneity: $r^2 = 0.36$, $f^2 = 43.2\%$, $H^2 = 1.80$ Test of $\theta_1 = \theta_1$ Q(2) = 3.56, $p = 0.00$ Toxic Test of $\theta_1 = \theta_1$ Q(2) = 3.24, $p = 0.07$ Overall Heterogeneity: $r^2 = 0.56$, $f^2 = 60.0\%$, $H^2 = 3.70$ Test of $\theta_1 = \theta_1$ Q(2) = 3.24, $p = 0.07$ Overall Heterogeneity: $r^2 = 11.10$, $I^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1$ Q(2) = 225.79, $p = 0.00$ Test of $\theta_2 = \theta_1$ Q(2) = 225.79, $p = 0.00$ Test of $\theta_1 = \theta_1$ Q(2) = 225.79, $p = 0.00$	Wang 2020	MSC	s	~30	R	1d		-6.58 [-10.03,	-3.12]	3.42
Wang 2020 MSC S -30 R 1d Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d J 2020 MSC M(3) H R 6d Heterogeneity: $t^2 = 6.36$, $t^2 = 90.44\%$, $t^2 = 10.46$ Test of $\theta_1 = \theta_1$ Q(9) = 71.62, $p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 MSC M(2) 100 R 3d Grange 2019 MSC M(3) 100 M# 5w Ebrahim 2018 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Zhong 2019 MSC M(6) -40 M# 2w ⁴ Duan 2020 MSC M(12) 100 M 13w [#] Heterogeneity: $t^2 = 25.17$, $t^2 = 90.06\%$, $t^2 = 51.43$ Test of $\theta_1 = \theta_1$ Q(9) = 132.86, $p = 0.00$ Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $t^2 = 0.54$, $t^2 = 4.32\%$, $t^2 = 1.61$, 0.361 4. -1.34 [-2.26 [-1.61 , 0.368] 4. -1.34 [-2.26 [-1.61 , 0.368] 4. -1.34 [-2.26 [-1.61 , 0.368] 4. -1.34 [-2.26 [-3.29 , -0.61] 4. -1.34 [-2.26 [-3.29 , -0.61] 4. -1.34 [-2.26 [-3.36 , $p = 0.00ToxicTest of \theta_1 = \theta_1 Q(2) -3.56, p = 0.17S6 NxHe 2012 MSC M(3) 30 M 2dVan Koppen 2012 MSC M(3) 100 M# 3dHeterogeneity: t^2 = 0.56, t^2 = 80.10\%, t^2 = 3.24Test of \theta_1 = \theta_1 Q(2) -3.24, p = 0.07OverallHeterogeneity: t^2 = -1.10, t^2 = 95.78\%, t^2 = 23.70Test of \theta_1 = \theta_1 Q(2) -3.24, p = 0.00Test of \theta_1 = \theta_1 Q(24) -2.25, \theta_1 = 0.07$	Wang 2020	MSC	S	~30	R	1d		-2.61 [-4.39,	-0.82]	4.07
Wang 2020 MSC S -30 R 1d Chen 2019 MSC S 200 M# 1d di 2020 MSC M(3) H R 6d Heterogeneity: $t^2 = 6.36$, $t^2 = 90.44\%$, $H^2 = 10.46$ Test of $\theta_1 = \theta_1^2 (Q) = 71.62$, $p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(5) 100 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Theterogeneity: $t^2 = 25.17$, $t^2 = 90.60$ Toxic Tamirez Bajo 2020 MSC M(2) 100 M 13w# Heterogeneity: $t^2 = 25.17$, $t^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2 (Q) = 13.286$, $p = 0.07$ Overall Heterogeneity: $t^2 = 1.10$, $t^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2 (Q 2) = 3.56$, $p^2 = 0.00$ Test of $\theta_1 = \theta_1^2 (Q 2) = 3.56$, $p = 0.00$ Toxic Test of $\theta_1 = \theta_1^2 (Q 2) = 3.56$, $p = 0.07$ Overall Heterogeneity: $t^2 = 1.10$, $t^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2 (Q 2) = 25.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2 (Q 2) = 25.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2 (Q 2) = 25.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2 (Q 2) = 25.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2 (Q 2) = 25.79$, $p = 0.00$	Wang 2020	MSC	s	~30	R	1d	-	-0.15 [-1.39,	1.10]	4.22
Chen 2019 MSC S 200 M# 1d J = 220 MSC M(3) H R 6d Heterogeneity: $\tau^2 = 6.36$, $J^2 = 90.44\%$, $H^2 = 10.46$ Test of $\theta_1 = \theta_1^2 Q(9) = 71.62$, $p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 MSC M(5) 100 M# 5w Cheng 2019 MSC M(5) 100 M# 2w Cheng 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(12) 100 M 13w# Theterogeneity: $\tau^2 = 25.17$, $J = 90.69$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1^2 Q(9) = 132.86$, $p = 0.00$ Texic Texic Texic $\theta_1 = \theta_1^2 Q(9) = 132.86$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 0.34$, $J^2 = 4.32\%$, $H^2 = 1.80$ Test of $\theta_1 = \theta_1^2 Q(2) = 3.56$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 0.34$, $J^2 = 4.32\%$, $H^2 = 1.80$ Test of $\theta_1 = \theta_1^2 Q(2) = 3.56$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 0.34$, $J^2 = 4.32\%$, $H^2 = 1.80$ Test of $\theta_1 = \theta_1^2 Q(2) = 3.56$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 0.34$, $J^2 = 4.32\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2 Q(2) = 25.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2 Q(2) = 25.79$, $p = 0.00$	Wang 2020	MSC	S	~30	R	1d	-	0.56 [-0.71,	1.84]	4.22
Ji 2020 MSC M(3) H R 6d Heterogeneity: $\tau^2 = 636$, $t^2 = 90.44\%$, $t^2 = 10.46$ Test of $\theta_1 = \theta_1 C(9) = 71.62$, $p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Ebrahim 2018 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(56) ~30 R# 9w Zhong 2019 MSC M(6) ~40 M# 2w Lorang 2019 MSC M(6) ~40 M# 2w The second of the	Chen 2019	MSC	S	200	M#	1d		-0.19 [-1.24,	0.86]	4.27
Heterogeneity: $r^{2} = 6.36$, $l^{2} = 90.44\%$, $H^{2} = 10.46$ Test of $\theta_{1} = \theta_{1}$: $Cq(9) = 71.62$, $p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(6) -30 R# 9w Zhong 2019 MSC M(6) -40 M# 2w* Zhong 2019 MSC M(6) -40 M# 2w* Zhong 2019 MSC M(6) -40 M# 2w* Zhong 2019 MSC M(6) -40 M# 2w* Duan 2020 MSC M(2) 100 M 13w# Heterogeneity: $r^{2} = 25.17$, $l^{2} = 98.06\%$, $H^{2} = 51.43$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.56$, $p = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.56$, $p = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.56$, $p = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{1} = 32.70$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $p = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\mu_{2} = 3.70$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\mu_{2} = 3.70$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.57$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\psi_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$ Test of $\theta_{1} = \theta_{1}$: $Cq(2) = 3.27$, $\theta_{2} = 0.00$	Ji 2020	MSC	M(3)	н	R	6d		-7.62 [-10.13,	-5.12]	3.81
Test of $\theta_{1} = \theta_{1}^{2} Q(9) = 71.62, p = 0.00$ Diabetes Duan 2019 USC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 HLSC M(5) 100 M# 5w Ebrahim 2018 MSC M(6) ~30 R# 9w Zhong 2019 MSC M(6) ~40 M# 2w Zhong 2019 MSC M(6) ~40 M# 2w Zhong 2019 MSC M(6) ~40 M# 2w Zhong 2019 MSC M(12) 100 M 13w# Heterogeneity: $\tau^{2} = 25.17, l^{2} = 98.06\%, H^{2} = 51.43$ Test of $\theta_{1} = \theta_{1}^{2} Q(9) = 132.86, p = 0.17$ 56 Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $\tau^{2} = 0.34, l^{2} = 44.32\%, H^{2} = 3.24$ Test of $\theta_{1} = \theta_{1}^{2} Q(2) = 3.56, p = 0.17$ 56 Nx Heterogeneity: $\tau^{2} = 1.1.0, l^{2} = 95.78\%, H^{2} = 23.70$ Test of $\theta_{1} = \theta_{1}^{2} Q(2) = 225.79, p = 0.00$ Test of $\theta_{1} = \theta_{1}^{2} Q(2) = 225.79, p = 0.00$ Test of $\theta_{1} = \theta_{1}^{2} Q(2) = 225.79, p = 0.00$	Heterogeneity: $\tau^2 = 6.3$	36, l ² = 90.4	44%, H ² :	= 10.46			•	-2.88 [-4.56,	-1.20]	
Diabetes Duan 2019 uSC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 HLSC M(5) 100 M# 5w Ebrahim 2018 MSC M(56) -30 R# 9w Zhong 2019 MSC M(4) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(12) 100 M 13w# Heterogeneity: $r^2 = 25.17$, $l^2 = 98.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$: Q(9) = 132.86, p = 0.00 Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Heterogeneity: $r^2 = 0.34$, $l^2 = 44.32\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1$: Q(2) = 3.56, p = 0.17 SK Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $r^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1$: Q(2) = 2.55.7, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.55.79, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00 Test of $\theta_1 = \theta_1$: Q(2) = 2.57.9, p = 0.00	Test of $\theta_i = \theta_j$: Q(9) = 7	71.62, p = 0	0.00				•				
Duan 2019 USC M(12) 100 R 3d Jang 2016 USC M(12) 100 R 3d Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(56)30 R# 9w Zhong 2019 MSC M(6)40 M# 2w Thong 2019 MSC M(6)40 M# 2w Duan 2020 MSC M(12) 100 M 13w# Jin 2019 MSC M(12) 100 M 13w# Heterogeneity: $r^2 = 25.17$, $l^2 = 98.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1^2$ C(9) = 132.86, p = 0.00 Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Heterogeneity: $r^2 = 0.34$, $l^2 = 43.32\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1^2$ C(2) = 3.56, p = 0.07 Toxic Heterogeneity: $r^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2$ C(2) = 225.79, p = 0.00 Test of $\theta_1 = \theta_1^2$ C(2) = 122.879, p = 0.00 Test of $\theta_1 = \theta_1^2$ C(2) = 11.51, p = 0.01	Dishotos										
Later Let $C = C = C = C = C = C = C = C = C = C $	Duan 2019	use	M(12)	100	в	3d		-2 84 1	-4.06	-1 621	4 23
Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 HLSC M(5) 100 M# 5w Grange 2019 MSC M(5) 100 M# 5w Ebrahim 2018 MSC M(66) -30 R# 9w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(6) -40 M# 2w Zhong 2019 MSC M(12) 100 M 13w# Jin 2019 MSC M(12) 100 M 13w# Heterogeneity: $t^2 = 25.17$, $t^2 = 98.06\%$, $t^2 = 51.43$ Tast of $\theta_1 = \theta_1$; Q(9) = 132.86, p = 0.00 Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Heterogeneity: $t^2 = 0.34$, $t^2 = 44.32\%$, $t^2 = 1.80$ Tast of $\theta_1 = \theta_1$; Q(2) = 3.56, p = 0.07 S/6 Nx He decrogeneity: $t^2 = 0.56$, $t^2 = 69.10\%$, $t^2 = 23.70$ Test of $\theta_1 = \theta_1$; Q(2) = 3.56, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 3.56, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00 Test of $\theta_1 = \theta_1$; Q(2) = 25.78, p = 0.00	liano 2016	1150	M(12)	100	B	34		0 90 1	0.02	1 781	4 30
$\begin{aligned} & \text{Grange 2019} & \text{MSC} & \text{M(5)} & 100 & \text{M#} & 5w \\ & \text{Grange 2019} & \text{MSC} & \text{M(5)} & 100 & \text{M#} & 5w \\ & \text{Ebrahim 2018} & \text{MSC} & \text{M(5)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(6)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(6)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(6)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(6)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(6)} & -40 & \text{M#} & 2w^* \\ & \text{Zhong 2019} & \text{MSC} & \text{M(12)} & 100 & \text{M} & 13w\# \\ & \text{Duan 2020} & \text{MSC} & \text{M(12)} & 100 & \text{M} & 13w\# \\ & \text{Heterogeneity: } \tau^2 = 25.17, l^2 = 98.06\%, H^2 = 51.43 \\ & \text{Test of } \theta_1 = \theta_1; Q(9) = 132.86, p = 0.00 \\ & \text{Toxic} \\ & \text{Ramirez Bajo 2020} & \text{MSC} & \text{M(2)} & 100 & \text{M} & 1d \\ & \text{Heterogeneity: } \tau^2 = 0.34, l^2 = 44.32\%, H^2 = 1.80 \\ & \text{Test of } \theta_1 = \theta_1; Q(2) = 3.56, p = 0.17 \\ & \text{S'6 Nx} \\ & \text{He 2012} & \text{MSC} & \text{M(3)} & 30 & \text{M} & 2d \\ & \text{Van Koppen 2012} & \text{MSC} & \text{M(4)} & 7 & \text{R} & 7w \\ & \text{Heterogeneity: } \tau^2 = 0.56, l^2 = 69.10\%, H^2 = 3.24 \\ & \text{Test of } \theta_1 = \theta_1; Q(24) = 225.79, p = 0.00 \\ & \text{Test of } \theta_1 = \theta_1; Q(24) = 225.79, p = 0.00 \\ & \text{Test of } \theta_1 = \theta_1; Q(24) = 225.79, p = 0.00 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Heterogeneity: } \tau^2 = 11.10, l^2 = 95.78\%, H^2 = 23.70 \\ & \text{Test of } \theta_1 = \theta_1; Q(24) = 225.79, p = 0.00 \\ & \text{Test of } group differences: Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, p = 0.01 \\ & \text{Test of group differences: } Q_n(3) = 11.51, $	Grance 2019	HISC	M(5)	100	M#	50		-0.50[-1.63	0.621	4 25
Lange 2015 in dec m(4) references: $Q_{6}(3) = 43.24$ in dec m(4) references: $Q_{6}(3) = 11.51$, $p = 0.01$ is defined as the decomposite in the decomposite	Grange 2019	MSC	M(5)	100	M#	5.		-0.24 [-1.35	0.871	4 25
Laramin 2010 MIG (M(2)) -40 M# 2w Zhong 2019 MIG (M(4) ~40 M# 2w -10.65 [-14.23, -7.06] 3. -7.99 [-10.74, -5.24] 3. -7.99 [-10.74, -5.24] 3. -7.99 [-10.74, -5.24] 3. -7.99 [-10.74, -5.24] 3. -1.06 [-1.96, -0.16] 4. -1.06 [-1.96, -0.16] 4. -6.93 [-5.96, -9.9, -3.97] 3. -1.06 [-1.96, -0.16] 4. -4.52 [-7.73, -1.32] Toxic Ramirez Bajo 2020 MISC M(2) 100 M 1d Famirez Bajo 2020 MISC M(2) 100 M 2w Kholia, 2020 MISC M(2) 100 M 2w Heterogeneity: $r^2 = 0.34$, $l^2 = 44.32\%$, $h^2 = 1.80$ Test of $\theta_i = \theta_i$: Q(2) = 3.56, $p = 0.17$ 5/6 Nx He 2012 MISC M(3) 30 M 2d Van Koppen 2012 MISC M(4) 7 R 7w Heterogeneity: $r^2 = 0.56$, $l^2 = 69.10\%$, $h^2 = 3.24$ Test of $\theta_i = \theta_i$: Q(1) = 3.24, $p = 0.07$ Overall Heterogeneity: $r^2 = 11.10$, $l^2 = 95.78\%$, $h^2 = 23.70$ Test of $\theta_i = \theta_i$: Q(2) = 225.79, $p = 0.00$ Test of $\theta_i = \theta_i$: Q(2) = 225.79, $p = 0.00$ Test of $\theta_i = \theta_i$: Q(2) = 225.79, $p = 0.00$	Ebrahim 2018	MSC	M(56)	-30	R#	Gw		_2 01 [-4.36	-1.451	4 17
Link Color Constant of the co	Zhong 2019	MSC	M(4)	~40	M#	2w*		-10.65 [-14 23	-7.061	3.36
The second problem of	Zhong 2019	MSC	M(6)	~40	M#	2w*	_	-7.99 [-10 74	-5 241	3 72
The second seco	Zhong 2019	MSC	M(8)	~40	M#	2w*	←	-17.05 [-22.68	-11 41]	2.51
$\begin{aligned} & \text{Line 2D2} & \text{MSC} M(12) n.a. M 13w\# \\ & \text{Heterogeneity: } \tau^2 = 25.77, \ l^2 = 98.06\%, \ H^2 = 51.43 \\ & \text{Test of } \theta_i = \theta_i; \ Q(9) = 132.86, \ p = 0.00 \end{aligned}$	Duan 2020	MSC	M(12)	100	M	13w#		-6.93 [-9.89	-3.971	3.63
Heterogeneity: $r^2 = 25.17$, $i^2 = 98.06\%$, $H^2 = 51.43$ Test of $\theta_1 = \theta_1^{-} Q(9) = 132.86$, $p = 0.00$ Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $r^2 = 0.34$, $i^2 = 44.32\%$, $H^2 = 1.80$ Test of $\theta_1 = \theta_1^{-} Q(2) = 3.56$, $p = 0.17$ 5/6 Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $r^2 = 0.56$, $i^2 = 69.10\%$, $H^2 = 3.24$ Test of $\theta_1 = \theta_1^{-} Q(1) = 3.24$, $p = 0.07$ Overall Heterogeneity: $r^2 = 11.10$, $i^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^{-} Q(24) = 225.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^{-} Q(24) = 225.79$, $p = 0.00$	Jin 2019	MSC	M(12)	na	м	13w#		-1.06 [-1.96	-0.16]	4.30
Test of $\theta_1 = \theta_1^{-} Q(\theta) = 132.86$, $p = 0.00$ Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $\tau^2 = 0.34$, $t^2 = 44.32\%$, $t^2 = 1.80$ Test of $\theta_1 = \theta_1^{-} Q(2) = 3.56$, $p = 0.17$ 5/6 Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $\tau^2 = 0.56$, $t^2 = 69.10\%$, $t^2 = 3.24$ Test of $\theta_1 = \theta_1^{-} Q(1) = 3.24$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 11.10$, $t^2 = 95.78\%$, $t^2 = 23.70$ Test of $\theta_1 = \theta_1^{-} Q(24) = 225.79$, $p = 0.00$ Test of group differences: $Q_n(3) = 11.51$, $p = 0.01$	Heterogeneity: $\tau^2 = 25$.17. l ² = 98	.06%. H ²	= 51.43			-	-4.52 [-7.73	-1.32]	
Toxic Ramirez Bajo 2020 MSC M(2) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $\tau^2 = 0.34$, $t^2 = 44.32\%$, $H^2 = 1.80$ -2.05 [-3.29, -0.81] 4. Test of $\theta_i = \theta_i$; Q(2) = 3.56, p = 0.17 -7.25 [-2.24, -0.26] -1.25 [-2.24, -0.26] S/6 Nx -0.63 [-1.61, 0.35] 4. -0.63 [-1.61, 0.35] 4. Van Koppen 2012 MSC M(4) 7 R 7w -0.64 [-0.34, 1.63] 4. Heterogeneity: $\tau^2 = 0.56$, $t^2 = 69.10\%$, $H^2 = 3.24$ 0.01 [-1.24, 1.26] -2.96 [-4.33, -1.60] Worrall -2.96 [-4.33, -1.60] -2.96 [-4.33, -1.60] Heterogeneity: $\tau^2 = 11.10$, $t^2 = 95.78\%$, $H^2 = 23.70$ -2.96 [-4.33, -1.60] Test of $\theta_i = \theta_i$; Q(24) = 225.79, p = 0.00 -2.96 [-4.33, -1.60]	Test of $\theta_i = \theta_j$: Q(9) =	132.86, p =	0.00								
Hamirez Bajo 2020 MSC M(2) 100 M 1d Ramirez Bajo 2020 MSC M(2) 100 M 2w Ramirez Bajo 2020 MSC M(2) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $\tau^2 = 0.34$, $t^2 = 44.32\%$, $t^2 = 1.80$ -2.05 [-3.29, -0.81] 4. Test of $\theta_1 = \theta_1^{\circ}$ Q(2) = 3.56, $p = 0.17$ -1.25 [-2.24, -0.25] -1.25 [-2.24, -0.25] S/6 Nx Heterogeneity: $\tau^2 = 0.56$, $t^2 = 69.10\%$, $H^2 = 3.24$ -0.63 [-1.61, 0.35] 4. Van Koppen 2012 MSC M(4) 7 R 7w -0.64 [-0.34, 1.63] 4. Heterogeneity: $\tau^2 = 0.56$, $t^2 = 69.10\%$, $H^2 = 3.24$ Test of $\theta_1 = \theta_1^{\circ}$ Q(1) = 3.24, $p = 0.07$ -2.96 [-4.33, -1.60] Heterogeneity: $\tau^2 = 11.10$, $t^2 = 95.78\%$, $H^2 = 23.70$ -2.96 [-4.33, -1.60] -2.96 [-4.33, -1.60] Test of $\theta_1 = \theta_1^{\circ}$ Q(2) = 225.79, $p = 0.00$ -2.96 [-4.33, -1.60] -2.96 [-4.33,	Toxio										
Haimez Dajo Zuzo MSC M(Z) 100 M 10 Ramirez Bajo 2020 MSC M(Z) 100 M 2w Ramirez Bajo 2020 MSC M(Z) 100 M 2w Kholia, 2020 MSC M(3) 100 M# 3d Heterogeneity: $\tau^2 = 0.34$, $l^2 = 44.32\%$, $l^2 = 1.80$ -2.05 [-3.29, -0.81] 4. Test of $\theta_1 = \theta_1^{\circ}$, Q(2) = 3.56, p = 0.17 -1.34 [-2.24, -0.25] -1.25 [-2.24, -0.25] 5/6 Nx Heterogeneity: $\tau^2 = 0.56$, $l^2 = 69.10\%$, $H^2 = 3.24$ -0.63 [-1.61, 0.35] 4. Van Koppen 2012 MSC M(4) 7 R 7w -0.64 [-0.34, 1.63] 4. Heterogeneity: $\tau^2 = 0.56$, $l^2 = 69.10\%$, $H^2 = 3.24$ 0.01 [-1.24, 1.26] -2.96 [-4.33, -1.60] Werall -2.96 [-4.33, -1.60] -2.96 [-4.33, -1.60] Heterogeneity: $\tau^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ -2.96 [-4.33, -1.60] -2.96 [-4.33, -1.60] -2.96 [Pamiraz Raia 2020	MSC	M(2)	100	м	14		1 95 0	-1.60	0 991	4 22
Intervention Integration Integration <td>Ramirez Bajo 2020</td> <td>MSC</td> <td>M(2)</td> <td>100</td> <td>M</td> <td>200</td> <td></td> <td>-0.30[</td> <td>-2.72</td> <td>0.001</td> <td>4.22</td>	Ramirez Bajo 2020	MSC	M(2)	100	M	200		-0.30[-2.72	0.001	4.22
Ninka, 2020 NiSC N(3) Ninka (10) Ninka (10) </td <td>Kholia 2020</td> <td>MSC</td> <td>M(2)</td> <td>100</td> <td>N/#</td> <td>24</td> <td>-</td> <td>-2.05 [</td> <td>-2.72,</td> <td>0.003</td> <td>4.00</td>	Kholia 2020	MSC	M(2)	100	N/#	24	-	-2.05 [-2.72,	0.003	4.00
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5/6 Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $\tau^2 = 0.56$, $l^2 = 69.10\%$, $H^2 = 3.24$ Test of $\theta_1 = \theta_1^{\circ}$ Q(1) = 3.24, p = 0.07 Overall Heterogeneity: $\tau^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^{\circ}$ Q(24) = 225.79, p = 0.00 Test of $\theta_1 = \theta_1^{\circ}$ Q(24) = 225.79, p = 0.00	Test of $\theta_i = \theta_i$: Q(2) = 3	3.56, p = 0.	17	- 1.00			×.	1.20 [2.24,	0.20]	
5/6 Nx He 2012 MSC M(3) 30 M 2d Van Koppen 2012 MSC M(4) 7 R 7w Heterogeneity: $\tau^2 = 0.56$, $l^2 = 69.10\%$, $H^2 = 3.24$ 0.01 [-1.24, 1.26] 0.01 [-1.24, 1.26] Test of $\theta_i = \theta_i$: Q(1) = 3.24, p = 0.07 -2.96 [-4.33, -1.60] -2.96 [-4.33, -1.60] Test of $\theta_i = \theta_i$: Q(24) = 225.79, p = 0.00 Test of group differences: Q ₀ (3) = 11.51, p = 0.01 -2.96 [-4.33, -1.60]											
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Van Koppen 2012 MSC M(4) 7 R 7w 0.64 [-0.34, 1.63] 4. Heterogeneity: $\tau^2 = 0.56$, $l^2 = 69.10\%$, $H^2 = 3.24$ 0.01 [-1.24, 1.26] Test of $\theta_i = \theta_i$: Q(1) = 3.24, p = 0.07 Overall -2.96 [-4.33, -1.60] Heterogeneity: $\tau^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_i = \theta_i$: Q(24) = 225.79, p = 0.00 Test of $\theta_i = \theta_i$: Q(3) = 11.51, p = 0.01	He 2012	MSC	M(3)	30	м	2d		-0.63 [-1.61,	0.35]	4.28
Heterogeneity: $r = 0.56$, $r = 09.10\%$, $H^2 = 3.24$ Test of $\theta_1 = \theta_1^2$, $Q(1) = 3.24$, $p = 0.07$ Overall Heterogeneity: $r^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_1 = \theta_1^2$, $Q(24) = 225.79$, $p = 0.00$ Test of $\theta_1 = \theta_1^2$, $Q(24) = 225.79$, $p = 0.00$	Van Koppen 2012	MSC	M(4)	7	R	7w		0.64 [-0.34,	1.63]	4.28
less of $\theta_i = \theta_i^*$, $Q(1) = 3.24$, $p = 0.07$ Overall Heterogeneity: $\tau^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_i = \theta_i^*$, $Q(24) = 225.79$, $p = 0.00$ Test of group differences: $Q_p(3) = 11.51$, $p = 0.01$	Heterogeneity: $\tau^2 = 0.8$	56, l ^e = 69.	10%, H ² :	= 3.24			•	0.01 [-1.24,	1.26]	
Overall -2.96 [-4.33, -1.60] Heterogeneity: τ² = 11.10, l² = 95.78%, H² = 23.70 -2.96 [-4.33, -1.60] Test of θ ₁ = θ ₁ ; Q(24) = 225.79, p = 0.00 -2.96 [-4.33, -1.60] Test of group differences: Q ₀ (3) = 11.51, p = 0.01 -2.96 [-4.33, -1.60]	Test of $\theta_i = \theta_j$: Q(1) = 3	3.24, p = 0.	07								
Heterogeneity: $\tau^2 = 11.10$, $l^2 = 95.78\%$, $H^2 = 23.70$ Test of $\theta_i = \theta_j$: Q(24) = 225.79, p = 0.00 Test of group differences: Q ₀ (3) = 11.51, p = 0.01	Overall						•	-2.96 [-4.33,	-1.60]	
Test of $\theta_i = \theta_i$; Q(24) = 225.79, p = 0.00 Test of group differences: Q ₀ (3) = 11.51, p = 0.01	Heterogeneity: $\tau^2 = 11$.10, l ² = 95	. 78%, H ²	= 23.70)						
Test of group differences: Q ₀ (3) = 11.51, p = 0.01	Test of $\theta_i = \theta_j$: Q(24) =	225.79, p	= 0.00								
	Test of group difference	es: Q _b (3) =	: 11.51, p	= 0.01							
-20 -15 -10 -5 0						3	20 -15 -10 -5 0	_			

B. The effect of EV-based treatement on plasma urea for all studies in CKD

Random-effects REML model Sorted by: order **Supplementary figure 4;** Subgroup analyses conducted for all study cohorts: standardized mean difference (SMD) in (A) serum creatinine and (B) urea. Data represent SMD calculated based on different factors, with the 95% confidence interval (95% CI). RE, random effect.

A. Dif	ferences in serum creatinine ac	orrding to EV trreatement and model related fact	ors
Subgroup	Study cohorts	SMD with 95% Cl	P-value
Therapy			
Preventive	14	-1.41 [-2.62, -0.2] 0.022
Curative	13	-7.33 [-12.80, -1.86	0.009
Test of group d	ifferences: $Q_{b}(1) = 4.29$, p = 0.04		
Dose			
Single	13	-1.61 [-3.06, -0.16	6] 0.029
Multiple	14	-6.72 [-11.77, -1.67] 0.009
Test of group d	ifferences: $Q_{b}(1) = 3.62$, p = 0.06		
Transplant			
Allogenic	15	-2.53 [-4.26, -0.79	0.004
Xenogenic	12	-6.67 [-12.84, -0.50	0.034
Test of group d	ifferences: $Q_{b}(1) = 1.61$, p = 0.20		
Etiology due t	o DM		
No	17	-1.72 [-2.77, -0.67] 0.001
Yes	10	-8.97 [-16.41, -1.53	0.018
Test of group d	ifferences: $Q_{b}(1) = 3.57$, p = 0.06		
Animal			
Mouse	17	-6.63 [-10.86, -2.40	0.002
Rat	8	-0.91 [-2.63, 0.82	.303
Pig	2	-1.10 [-1.88, -0.33	0.005
Test of group d	ifferences: $Q_{b}(2) = 6.49$, p = 0.04		
Overall		-4.00 [-6.37, -1.64] 0.001
Heterogeneity:	$\tau^2 = 36.74, I^2 = 98.76\%, H^2 = 80.79$		
Test of $\theta_i = \theta_j$:	Q(26) = 240.39, p = 0.00		
		-15 -10 -5 0	
landom-effects	REML model		

			SMD	
Subgroup	Study cohorts		with 95% CI	P-value
Therapy				
Preventive	15	•	-2.17 [-3.37, -0.96]	0.000
Curative	10	•	-4.40 [-7.64, -1.16]	0.008
Test of group diffe	erences: Q _b (1) = 1.61, p = 0.20			
Dose				
Multiple	16	•	-3.39 [-5.50, -1.28]	0.002
Single	9	_	-2.33 [-3.81, -0.85]	0.002
Test of group diffe	rences: Q _b (1) = 0.66, p = 0.42			
Transplant				
Allogenic	14	_	-2.29 [-3.39, -1.20]	0.000
Xenogenic	11	•	-3.95 [-7.05, -0.85]	0.013
Test of group diffe	rences: $Q_{b}(1) = 0.97$, p = 0.32			
Animai				
Mouse	16		-3.53 [-5.45, -1.61]	0.000
Rat	9		-2.07 [-4.00, -0.13]	0.036
Test of group diffe	rences: $Q_{b}(1) = 1.11$, p = 0.29			
Etiology due to I	м			
No	15	e	-2.07 [-3.260.89]	0.001
Yes	10		-4.52 [-7.73, -1.32]	0.006
Test of group diffe	rences: Q,(1) = 1.97, p = 0.16			
Overall			-2.96 [-4.33, -1.60]	0.000
Heterogeneity: τ^2	= 11.10, l ² = 95.78%, H ² = 23.70			
Test of $\theta_i = \theta_j$: Q(2)	24) = 225.79, p = 0.00			
		-8 -6 -4 -2 () D	

B. Differences in urea according to EV treatement- and model-related factors