Table S1. Search strategies used for systematic review

Database/Registry	**Search criteria (09/05/2019 – 09/08/2020)**	**Search criteria (09/08/2020 only)**
Cochrane Library	*Search #1*: ascorbic acid AND diabetes and limit to Trials tab; *Search #2*: "vitamin C" AND diabetes and limit to Trials tab	-
Scopus	*Search #1*: ascorb* AND diabetes AND random*; *Search #2*: "vitamin C" AND diabetes AND random*; *Search #3*: ascorb* AND supplementation AND diabetes; *Search #4*: "vitamin C" AND supplementation AND diabetes	('Ascorbic Acid'[Mesh] OR ('Vitamin C') OR ('Vit C') OR ascorb* OR dehydroascorb*) AND *1*. (MODY or NIDDM or T2D*).[text words]. *2*. (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).[text words]. *3*. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).[text words]. AND ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[title/abstract] OR randomised[title/abstract]) OR (placebo[title/abstract]) OR (drug therapy[subject heading]) OR (randomly[title/abstract]) OR (trial[title/abstract]) OR (groups[title/abstract])) AND NOT (animals)
Embase	*Search #1*: 'ascorbic acid' AND diabetes (and limit search to randomized controlled trials only in the study selection option; *Search #2*: 'vitamin C' AND diabetes (and limit search to randomized controlled trials only in the study selection option	As above
MEDLINE-Pubmed	*Search #1*: ascorb* AND diabetes AND random*; *Search #2*: "vitamin C" AND diabetes AND random*; *Search #3*: ascorb* AND supplementation AND diabetes; *Search #4*: "vitamin C" AND supplementation AND diabetes	As above
Clinical trial registries	ClinicalTrials.gov: Search #1: condition: diabetes; other terms:	-

	ascorbic acid; Search #2: condition: diabetes; other terms: vitamin C. ANZCTR Search #1: ascorbic acid; Search #2: ascorb* AND diabetes. EU Clinical Trial Register: Search #1: ascorbic acid; Search #2: “vitamin C”; ISRCTN registry: Search #1: ascorbic acid AND diabetes; Search #2: “vitamin C” AND diabetes	

Table S2: Sensitivity analyses

Analysis	Vitamin C vs. control/ placebo	HbA1c (%)	Fasting glucose (mmol/L)	Postprandial glucose (mmol/L)	Fasting Insulin (µU/mL)	HOMA-IR	Insulin sensitivity * (clamp)	Trigs (mmol/L)	Total C † (mmol/L)	LDL-C † (mmol/L)	HDL-C † (mmol/L)	SBP (mm Hg)	DBP (mm Hg)	MDA *	F_2-Isoprostanes *	LDL-oxidation *
Main analysis	Effect [95% CI]	-0.54 [-0.90, -0.17]	-0.74 [-1.17, -0.31]	-0.95 [-1.83, -0.06]	-1.43 [-2.88, 0.01]	-0.74 [-2.09, 0.61]	1.97 [-0.90, 4.84]	-0.20 [-0.36, -0.04]	-0.27 [-0.43, -0.10]	-0.23 [-0.48, 0.03]	0.06 [-0.00, 0.13]	-6.27 [-9.60, -2.95]	-3.77 [-6.13, -1.42]	-1.25 [-1.88, -0.62]	-0.22 [-0.61, 0.16]	0.24 [-0.23, 0.71]
	P value	0.004	0.0007	0.04	0.05	0.28	0.18	0.01	0.001	0.08	0.06	0.0002	0.002	0.0001	0.26	0.32
	n studies	16	20	4	9	5	3	17	19	16	17	8	8	5	3	3
	n	1133	1305	235	436	263	86	1065	1125	988	1022	466	466	220	103	102
With added studies with no post-treatment data	Effect [95% CI]	-0.47 [-0.81, -0.14]	-0.59 [-0.97, -0.21]	-0.95 [-1.83, -0.06]	-1.31 [-2.65, 0.03]	-0.74 [-2.09, 0.61]	1.97 [-0.90, 4.84]	-0.18 [-0.33, -0.04]	-0.23 [-0.38, -0.08]	-0.19 [-0.41, 0.03]	0.05 [-0.00, 0.11]	-6.11 [-9.31, -2.92]	-3.70 [-5.97, -1.42]	-1.25 [-1.88, -0.62]	-0.22 [-0.61, 0.16]	0.24 [-0.23, 0.71]
	P value	0.006	0.002	0.04	0.06	0.28	0.18	0.01	0.002	0.10	0.06	0.0002	0.001	0.0001	0.26	0.32
	n studies	18	25	4	10	5	3	20	22	19	20	9	9	5	3	3
	n	1199	1515	235	466	263	86	1166	1226	1089	1123	491	491	220	103	102
Using a 0.5 correlation coefficient in calculations	Effect [95% CI]	-0.54 [-0.90, -0.18]	-0.76 [-1.19, -0.32]	-0.95 [-1.83, 0.06]	-1.34 [-2.68, -0.00]	-0.68 [-2.01, 0.66]	1.63 [-0.82, 4.07]	-0.20 [-0.36, -0.04]	-0.24 [-0.40, -0.08]	-0.22 [-0.47, 0.03]	0.06 [-0.00, 0.12]	-6.09 [-9.26, -2.92]	-4.11 [-6.34, -1.89]	-1.14 [-1.72, -0.57]	-0.20 [-0.59, 0.18]	0.18 [-0.24, 0.60]
	P value	0.003	0.0007	0.04	0.05	.32	0.19	0.01	0.003	0.09	0.05	0.0002	0.0003	<0.0001	0.30	0.39
	n studies	16	20	4	9	5	3	17	19	16	17	8	8	5	3	3
	n	1133	1305	235	436	263	86	1065	1125	988	1022	466	466	220	103	102
Low risk only‡ (random sequence generation)	Effect [95% CI]	-0.50 [-0.81, -0.19]	-1.05 [-1.49, -0.62]	-1.17 [-2.60, 0.26]	-1.68 [-2.63, -0.74]	-0.69 [-2.13, 0.76]	0.97 [-0.16, 2.11]	-0.14 [-0.34, 0.06]	-0.19 [-0.41, 0.03]	-0.26 [-0.59, 0.07]	0.04 [-0.03, 0.11]	-7.91 [-11.55, -4.27]	-5.18 [-7.33, -3.03]	-0.73 [-1.85, 0.39]	-0.19 [-0.67, 0.29]	No studies
	P value	0.001	<0.0001	0.11	0.0005	0.35	0.09	0.16	0.13	0.12	0.26	<0.0001	<0.0001	0.20	0.44	
	n studies	9	9	2	4	2	1	7	8	7	7	5	5	2	2	
	n	575	575	120	201	133	14	374	399	374	374	381	381	133	68	

Analysis	Vitamin C vs. control/ placebo	HbA1c (%)	Fasting glucose (mmol/L)	Postprandial glucose (mmol/L)	Fasting Insulin (µU/mL)	HOMA-IR	Insulin sensitivity (clamp)*	Trigs (mmol/L)	Total C † (mmol/L)	LDL-C † (mmol/L)	HDL-C † (mmol/L)	SBP (mm Hg)	DBP (mm Hg)	MDA*	F_{2}-Isoprostanes*	LDL-oxidation*
Low risk only‡ (allocation concealment)	Effect [95% CI]	-0.35 [-0.63, -0.06]	-0.80 [-1.46, -0.13]	-1.17 [-2.60, 0.26]	-0.74 [-2.72, 1.25]	-0.42 [-2.05, 1.22]	0.97 [-0.16, 2.11]	-0.09 [-0.28, 0.09]	-0.06 [-0.20, 0.09]	0.01 [-0.15, 0.17]	0.05 [-0.04, 0.14]	-4.90 [-9.93, 0.13]	-4.68 [-7.71, -1.66]	-1.27 [-1.70, -0.84]	-0.19 [-0.67, 0.29]	No studies
	P value	0.02	0.02	0.11	0.47	0.62	0.09	0.33	0.44	0.90	0.29	0.06	0.002	<0.0001	0.44	
	n studies	6	6	2	4	2	1	5	6	4	4	2	2	1	2	
	n	342	342	120	240	178	14	272	301	198	198	154	154	100	68	
Low risk only‡ (blinding of participants/ personnel)	Effect [95% CI]	-0.26 [-0.53, -0.00]	-0.21 [-0.82, 0.41]	-1.17 [-2.60, 0.26]	-1.01 [-2.51, 0.49]	-0.22 [-1.77, 1.33]	1.97 [-0.90, 4.84]	-0.16 [-0.35, 0.04]	-0.23 [-0.44, -0.02]	-0.08 [-0.34, 0.18]	0.05 [-0.03, 0.12]	-5.51 [-9.00, -2.01]	-4.74 [-6.54, -2.94]	-1.45 [-1.94, -0.96]	-0.22 [-0.61, 0.16]	0.44 [-0.05, 0.93]
	P value	0.05	0.51	0.11	0.19	0.78	0.18	0.11	0.03	0.56	0.23	0.002	<0.0001	<0.0001	0.26	0.08
	n studies	9	10	2	6	3	3	7	7	5	6	5	5	2	3	2
	n	491	523	120	352	210	86	390	394	282	316	303	303	140	103	70
Low risk only‡ (blinding of outcome assessment)	Effect [95% CI]	-0.34 [-0.67, 0.00]	-0.40 [-1.34, 0.54]	-1.21 [-2.45, 0.04]	-1.73 [-2.67, -0.78]	-1.24 [-1.75, -0.73]	0.97 [-0.16, 2.11]	-0.07 [-0.30, 0.17]	-0.17 [-0.35, 0.00]	-0.04 [-0.20, 0.13]	0.05 [-0.04, 0.14]	-4.90 [-9.93, 0.13]	-4.68 [-7.71, -1.66]	-1.27 [-1.70, -0.84]	-0.19 [-0.67, 0.29]	0.20 [-0.65, 1.04]
	P value	0.05	0.41	0.06	0.0004	<0.0001	0.09	0.57	0.06	0.66	0.29	0.06	0.002	<0.0001	0.44	0.64
	n studies	5	5	3	3	1	1	5	5	4	5	2	2	1	2	2
	n	268	268	152	168	100	14	234	234	200	234	154	154	100	68	66
Low risk only‡ (incomplete outcome data)	Effect [95% CI]	-0.71 [-1.13, -0.29]	-0.72 [-1.22, -0.21]	-1.21 [-2.45, 0.04]	-1.41 [-3.11, 0.28]	-1.01 [-2.60, 0.59]	2.50 [-2.63, 7.63]	-0.25 [-0.44, -0.06]	-0.34 [-0.55, -0.12]	-0.33 [-0.67, 0.02]	0.10 [0.00, 0.19]	-6.01 [-9.80, -2.22]	-3.36 [-6.13, -0.60]	-1.49 [-1.90, -1.08]	-0.28 [-0.70, 0.13]	0.24 [-0.23, 0.71]
	P value	0.0009	0.005	0.06	0.10	0.22	0.34	0.01	0.002	0.06	0.04	0.002	0.02	<0.0001	0.18	0.32
	n studies	12	14	3	6	4	2	12	13	10	11	7	7	4	2	3
	n	1022	1080	152	358	230	72	871	822	763	797	382	382	187	89	102

Analysis	Vitamin C vs. control/ placebo	HbA1c (%)	Fasting glucose (mmol/L)	Postprandial glucose (mmol/L)	Fasting Insulin (µU/mL)	HOMA-IR	Insulin sensitivity * (clamp)	Trigs (mmol/L)	Total C † (mmol/L)	LDL-C † (mmol/L)	HDL-C † (mmol/L)	SBP (mm Hg)	DBP (mm Hg)	MDA *	F_2-Isoprostanes *	LDL-oxidation *
Low risk only‡ (selective reporting)	Effect [95% CI]	-0.56 [-0.97, -0.14]	-0.75 [-1.21, -0.28]	-0.95 [-1.83, -0.06]	-2.04 [-3.12, -0.96]	-1.17 [-2.87, 0.53]	1.97 [-0.90, 4.84]	-0.23 [-0.42, -0.05]	-0.28 [-0.50, -0.07]	-0.23 [-0.53, 0.07]	0.06 [-0.02, 0.14]	-5.56 [-9.09, -2.04]	-3.12 [-5.55, -0.70]	-1.07 [-1.73, -0.40]	-0.22 [-0.61, 0.16]	0.24 [-0.23, 0.71]
	P value	0.008	0.002	0.04	0.0002	0.18	0.18	0.01	0.01	0.14	0.12	0.002	0.01	0.002	0.26	0.32
	n studies	14	17	4	7	4	3	14	14	13	14	7	7	4	3	3
	n	996	1137	235	333	185	86	905	905	871	905	07	407	193	103	102
Low risk only‡ (other biases)	Effect [95% CI]	-0.25 [-0.45, -0.06]	-0.02 [-0.68, 0.65]	-1.17 [-2.60, 0.26]	-2.04 [-3.39, -0.68]	1.83 [-2.88, 6.54]	1.97 [-0.90, 4.84]	-0.10 [-0.53, 0.34]	-0.34 [-0.83, 0.15]	-0.29 [-0.91, 0.32]	0.00 [-0.07, 0.07]	-7.93 [-14.45, -1.41]	-6.06 [-10.24, -1.88]	-1.80 [-2.55, -1.06]	-0.19 [-0.67, 0.29]	0.61 [-0.08, 1.30]
	P value	0.01	0.96	0.11	0.003	0.45	0.18	0.67	0.18	0.35	0.99	0.02	0.005	<0.0001	0.44	0.09
	n studies	5	6	2	4	1	3	4	4	3	4	1	1	1	2	1
	n	248	280	120	180	32	86	182	182	148	182	54	54	40	68	34

* measured using standardized mean differences; † C- Cholesterol; ‡ includes only low risk of bias studies as determined by the specific criteria of the Cochrane risk of bias tool; MDA – malondialdehyde.

Table S3. Sub-group analyses of outcomes with >10 studies: Mean difference of vitamin C supplementation compared to control

Sub-group	Measures	HbA1c (%)	Fasting Glucose (mmol/L)	Triglycerides (mmol/L)	Total Cholesterol (mmol/L)	LDL-Cholesterol (mmol/L)	HDL-Cholesterol (mmol/L)
Vitamin C dose							
<1000 mg/day	Effect [95% CI]	-0.63 [-1.41, 0.15]	-0.81 [-1.57, -0.04]	-0.31 [-0.58, -0.05]	-0.38 [-0.62, -0.15]	-0.55 [-0.88, -0.22]	0.09 [-0.05, 0.24]
	P	0.11	0.04	0.02	<0.01	0.001	0.20
	n studies	7	9	7	9	7	7
	n participants	600	663	597	657	554	554
≥1000 mg/day	Effect [95% CI]	-0.42 [-0.68, -0.15]	-0.69 [-1.22, -0.16]	-0.11 [-0.30, 0.08]	-0.16 [-0.39, 0.07]	0.03 [-0.21, 0.27]	0.04 [-0.01, 0.09]
	P	0.002	0.01	0.25	0.17	0.81	0.09
	n studies	9	11	10	10	9	10
	n participants	533	642	468	468	434	468
	Sub-group P	0.61	0.81	0.23	0.18	0.005	0.49
Trial duration							
<12 weeks	Effect [95% CI]	-0.24 [-0.64, 0.17]	-0.45 [-1.18, 0.28]	-0.11 [-0.21, 0.00]	-0.13 [-0.26, -0.00]	0.06 [-0.16, 0.28]	0.04 [-0.03, 0.11]
	P	0.25	0.22	0.15	0.04	0.60	0.22
	n studies	7	11	10	12	9	10
	n participants	340	512	473	533	396	430
≥12 weeks	Effect [95% CI]	-0.79 [-1.36, -0.23]	-1.00 [-1.53, -0.47]	-0.35 [-0.63, -0.08]	-0.55 [-0.91, -0.19]	-0.55 [-0.90, -0.21]	0.10 [-0.01, 0.21]
	P	0.006	0.0002	0.01	0.003	0.002	0.06
	n studies	9	9	7	7	7	7
	n participants	793	793	592	592	592	592
	Sub-group P	0.11	0.23	0.10	0.03	0.003	0.39
Baseline BMI							
<30.0 kg/m^2	Effect [95% CI]	-0.75 [-1.25, -0.24]	-0.90 [-1.39, -0.41]	-0.21 [-0.39, -0.03]	-0.22 [-0.40, -0.05]	-0.21 [-0.52, 0.10]	0.09 [0.01, 0.17]
	P	0.004	0.0003	0.02	0.01	0.18	0.04
	n studies	10	12	13	13	12	12
	n participants	935	1044	964	718	890	890
≥30.0 kg/m^2	Effect [95% CI]	-0.27 [-0.91, 0.37]	-0.91 [-2.41, 0.59]	-0.21 [-0.51, 0.09]	-0.08 [-0.32, 0.16]	-0.28 [-0.83, 0.27]	-0.01 [-0.17, 0.14]
	P	0.41	0.24	0.18	0.51	0.32	0.85
	n studies	3	4	3	4	3	3
	n participants	67	99	67	92	67	67
	Sub-group P	0.25	1.00	0.98	0.35	0.82	0.23
Baseline vitamin C							
<23 µmol/L	Effect [95% CI]	-0.21 [-0.42, 0.00]	0.45 [-0.78, 1.68]	0.10 [-0.55, 0.75]	-0.40 [-0.83, 0.03]	No studies	0.00 [-0.22, 0.22]
	P	0.05	0.48	0.76	0.07		1

Sub-group	Measures	HbA1c (%)	Fasting Glucose (mmol/L)	Triglycerides (mmol/L)	Total Cholesterol (mmol/L)	LDL-Cholesterol (mmol/L)	HDL-Cholesterol (mmol/L)
	n studies	3	4	1	1		1
	n participants	131	163	34	34		34
≥23 µmol/L	Effect [95% CI]	-0.29 [-0.72, 0.13]	-0.64 [-1.20, -0.08]	-0.16 [-0.58, 0.26]	-0.19 [-0.54, 0.16]	-0.24 [-0.71, 0.24]	0.00 [-0.07, 0.07]
	P	0.18	0.03	0.45	0.30	0.33	0.96
	n studies	4	4	4	5	4	4
	n participants	283	283	180	205	180	180
	Sub-group P	0.74	0.12	0.51	0.45	N/A	0.99
Active control vs. Placebo							
Active control comparator	Effect [95% CI]	-0.38 [-0.82, 0.05]	-1.03 [-1.87, -0.18]	-0.08 [-0.25, 0.10]	-0.09 [-0.56, 0.38]	-0.05 [-0.62, 0.53]	0.03 [-0.10, 0.18]
	P	0.08	0.02	0.39	0.70	0.87	0.65
	n studies	3	5	5	5	5	5
	n participants	122	231	231	231	231	231
Placebo comparator	Effect [95% CI]	-0.57 [-0.99, -0.15]	-0.64 [-1.14, -0.14]	-0.25 [-0.44, -0.05]	-0.31 [-0.49, -0.14]	-0.30 [-0.60, 0.00]	0.08 [-0.07, 0.07]
	P	0.007	0.01	0.01	0.0004	0.05	0.06
	n studies	13	15	12	14	11	12
	n participants	1011	1074	834	894	757	791
	Sub-group P	0.54	0.44	0.20	0.38	0.45	0.54
Lower vs higher risk of bias							
<4 low risk of bias Cochrane domains	Effect [95% CI]	-0.64 [-1.27, -0.02]	-0.99 [-1.52, -0.46]	-0.22 [-0.42, -0.01]	-0.27 [-0.47, -0.07]	-0.22 [-0.55, 0.10]	0.07 [-0.02, 0.16]
	P	0.04	0.0002	0.04	0.008	0.17	0.13
	n studies	10	13	12	14	12	12
	n participants	785	925	783	843	740	740
≥4 low risk of bias Cochrane domains	Effect [95% CI]	-0.38 [-0.70, -0.07]	-0.25 [-1.05, 0.54]	-0.15 [-0.43, 0.13]	-0.28 [-0.61, 0.05]	-0.14 [-0.48, 0.19]	0.05 [-0.22, 0.22]
	P	0.03	0.53	0.29	0.10	0.41	0.28
	n studies	6	7	5	5	4	5
	n participants	348	380	282	282	248	282
	Sub-group P	0.46	0.13	0.70	0.90	0.73	0.79

Table S4. Meta-regression analyses of outcomes with >10 studies

Modifying factor	HbA1c (%)	Fasting Glucose (mmol/L)	Triglycerides (mmol/L)	Total Cholesterol (mmol/L)	LDL-Cholesterol (mmol/L)	HDL-Cholesterol (mmol/L)
Baseline HbA1c (%)						
β	-0.4725	-0.5768	-0.1867	-0.3239	-0.5535	0.0874
[95% CI]	[-0.8595, -0.0855]	[-1.0463, -0.1075]	[-0.3539, -0.0195]	[-0.4773, -0.1704]	[-0.7609, -0.3460]	[-0.0051, 0.1799]
P	0.017	0.016	0.029	0.000	0.005	0.064
n studies	16	18	15	16	13	14
I^2 (residual)	83.65	71.90	60.77	36.29	52.22	72.56
Vitamin C dose (mg/day)						
β	0.0001	0.0009	0.0001	0.0001	0.0007	-0.0001
[95% CI]	[-0.0005, 0.0008]	[0.0001, 0.0017]	[-0.0001, 0.0004]	[-0.0001, 0.0004]	[0.0002, 0.0030]	[-0.0002, 0.0001]
P	0.661	0.020	0.303	0.352	0.013	0.319
n studies	16	20	17	19	16	17
I^2 (residual)	88.76	71.84	73.02	63.06	79.12	67.79
Trial duration (days)						
β	-0.0062	-0.0050	-0.0026	-0.0033	-0.0036	0.0015
[95% CI]	[-0.0092, -0.0033]	[-0.0091, -0.0009]	[-0.0038, -0.0013]	[-0.0053, -0.0013]	[-0.0061, -0.0012]	[0.0008, 0.0023]
P	0.000	0.016	0.000	0.001	0.004	0.000
n studies	16	20	17	19	16	17
I^2 (residual)	74.12	66.23	41.33	45.22	74.43	50.06
Baseline Age (y)						
β	0.0423	0.0434	0.0073	0.0138	0.0026	-0.0118
[95% CI]	[-0.0043, 0.0889]	[-0.0142, 0.0949]	[-0.0136, 0.0283]	[-0.0124, 0.0400]	[-0.0337, 0.0389]	[-0.0222, -0.0014]
P	0.075	0.147	0.492	0.303	0.889	0.026
n studies	16	20	17	19	16	17
I^2 (residual)	86.04	72	74.54	60.92	83.46	65.74
Baseline BMI (kg/m^2)						
β	0.1347	0.1102	0.0389	0.0637	0.0204	-0.0440
[95% CI]	[-0.0055, 0.2749]	[-0.0279, 0.2482]	[-0.0290, 0.1068]	[-0.0178, 0.1452]	[-0.0915, 0.1323]	[-0.0665, -0.0214]
P	0.060	0.118	0.262	0.125	0.721	0.000
n studies	13	16	16	17	15	15
I^2 (residual)	83.98	67.59	72.93	63.42	85.58	43.98
Diabetes duration (y)						
β	0.2108	0.1171	0.0168	0.0061	0.0204	-0.0130
[95% CI]	[-0.0461, 0.4677]	[-0.1140, 0.3482]	[-0.0740, 0.1077]	[-0.0778, 0.0901]	[-0.0915, 0.1323]	[-0.0455, 0.0195]
P	0.108	0.321	0.717	0.886	0.721	0.432

Modifying factor	HbA1c (%)	Fasting Glucose (mmol/L)	Triglycerides (mmol/L)	Total Cholesterol (mmol/L)	LDL-Cholesterol (mmol/L)	HDL-Cholesterol (mmol/L)
n studies	10	13	13	14	12	13
I^2 (residual)	88.54	79	80.7	70.75	84.2	70.07
Sample size (n)						
β	-0.0091	-0.0073	-0.0034	-0.0042	-0.0045	0.0002
[95% CI]	[-0.0114, -0.0069]	[-0.0126, -0.0021]	[-0.0050, -0.0019]	[-0.0068, -0.0016]	[-0.0076, -0.0013]	[0.0011, 0.0029]
P	0.000	0.006	0.000	0.001	0.005	0.000
n studies	16	20	17	19	16	17
I^2 (residual)	33.92	60.26	39.24	47.37	75.15	46.62
Baseline vitamin C (µmol/L)						
β	0.0012	-0.0058	-0.0093	0.0055	0.0662	0.0018
[95% CI]	[-0.0160, 0.0185]	[-0.0576, 0.0461]	[-0.0521, 0.0335]	[-0.0147, 0.0256]	[-0.0715, 0.2039]	[-0.0058, 0.0094]
P	0.889	0.828	0.671	0.596	0.346	0.649
n studies	7	8	5	6	4	5
I^2 (residual)	33.83	66.42	81.19	57.43	71.63	0

Table S5. GRADE Evidence Profile for effect of vitamin C supplementation on glycemic control and cardiovascular risk factors in people with Type 2 diabetes

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin C**	**Control/ Placebo**	**Absolute (95% CI)**	**Certainty**	**Importance**
HbA1c (%)											
16	randomised trials	not serious [*]	serious [†]	serious [‡]	serious [§]	none	570	563	MD **0.54 lower** (0.90 lower to 0.17 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Fasting glucose (mmol/L)											
20	randomised trials	serious [‖]	serious [†]	serious [‡]	serious [§]	none	670	635	MD **0.74 lower** (1.17 lower to 0.31 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Systolic blood pressure (mmHg)											
8	randomised trials	not serious	not serious	serious [‡]	not serious	none	236	230	MD **6.27 lower** (9.6 lower to 2.95 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Diastolic blood pressure (mmHg)											
8	randomised trials	not serious	serious [†]	serious [‡]	serious [§]	none	236	230	MD **3.77 lower** (6.13 lower to 1.42 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Triglycerides (mmol/L)											
17	randomised trials	serious [‖]	serious [†]	serious [‡]	serious [#]	none	559	506	MD **0.2 lower** (0.36 lower to 0.04 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Total cholesterol (mmol/L)											

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin C**	**Control/ Placebo**	**Absolute (95% CI)**	**Certainty**	**Importance**
19	randomised trials	serious ‖	serious †	serious ‡	serious #	none	589	536	MD **0.27 lower** (0.43 lower to 0.1 lower)	⨁◯◯◯ VERY LOW	CRITICAL
LDL Cholesterol (mmol/L)											
16	randomised trials	not serious	serious †	serious ‡	serious #	none	522	466	MD **0.23 lower** (0.48 lower to 0.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HDL cholesterol (mmol/L)											
17	randomised trials	serious ‖	serious †	serious ‡	serious #	none	539	483	MD **0.06 higher** (0 to 0.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference; * Overall, findings alternated from significantly favoring vitamin C (5 domains) to borderline (p=0.05) significant effects (2 domains) when undertaking sensitivity analyses on the basis of different individual Cochrane Risk of Bias domains when using only low risk studies – a decision was made to not rate down for risk of bias due to this relative consistency; † Significant heterogeneity in meta-analysis (I^2 >50%); ‡ Surrogate outcome measure, not patient-important endpoint; § Upper bound 95% confidence interval of estimate outside of clinical meaningfulness; ‖ Overall findings alternated from significantly favoring vitamin C to null effects when undertaking sensitivity analyses on the basis of different individual Cochrane Risk of Bias domains when using only low risk studies; ¶ Overall findings alternated from significantly favoring vitamin C to null effects when undertaking sensitivity analyses on the basis of different individual Cochrane Risk of Bias domains (p<0.05 for all domains except for allocation concealment (p=0.06) and blinding of outcome assessment (p=0.06) when using only low risk-of-bias studies – a decision was made to not rate down for risk of bias due to this relative consistency; # Upper and/or lower bounds of 95% confidence interval not clinically meaningful.

Table S6. Adverse effects reported in included studies

Study	Effects in Vitamin C group	Effects in Control group
Dakhale et al. 2011 (41)	No adverse effects on renal or liver function	No adverse effects on renal or liver function
Devanandan et al. 2020 (49)	None reported	None reported
El-Aal et al. 2018 (50)	No adverse effects on renal or liver function	No adverse effects on renal or liver function
Foroghi et al. 2018 (48)	Seven participants complained of physical discomfort	None reported
Gillani et al. 2017 (18)	23 adverse events reported (2 hypoglycemic episodes; 3 hyperglycemic episodes; 5 wrong timing of medication intake); no adverse effects on renal or liver function	89 adverse events reported (30 hypoglycemic episode; 45 hyperglycemic episode; 11 wrong timing of medication); no adverse effects on renal or liver function
Kunsongkeit et al. (46)	None reported	None reported
Mason et al. 2016 (42)	Minor GI discomfort during first 1-2 weeks in one participant, after which time it disappeared; no adverse effects on renal or liver function	No adverse effects on renal or liver function
Mason et al. 2019 (5)	No adverse effects on renal or liver function	A “feeling of depression” reported in one participant; no adverse effects on renal or liver function
Paolisso et al. 1995 (6)	No adverse effects on renal or liver function	No adverse effects on renal or liver function
Ragheb et al. 2020 (59)	Survey Quality of Life scores reported significantly better role limitation to physical health and emotional problems when compared to control	-
Rekha et al. 2013 (21)	Some mild adverse effects such as nausea, vomiting, diarrhea, giddiness, headache, oral mucosal erosion and fatigue	Some mild adverse effects such as nausea, vomiting, diarrhea, giddiness, headache, oral mucosal erosion and fatigue
Sanguanwong et al. 2016 (20)	None reported	None reported
Siavash et al. 2014 (47)	Measured, but not reported	Measured, but not reported

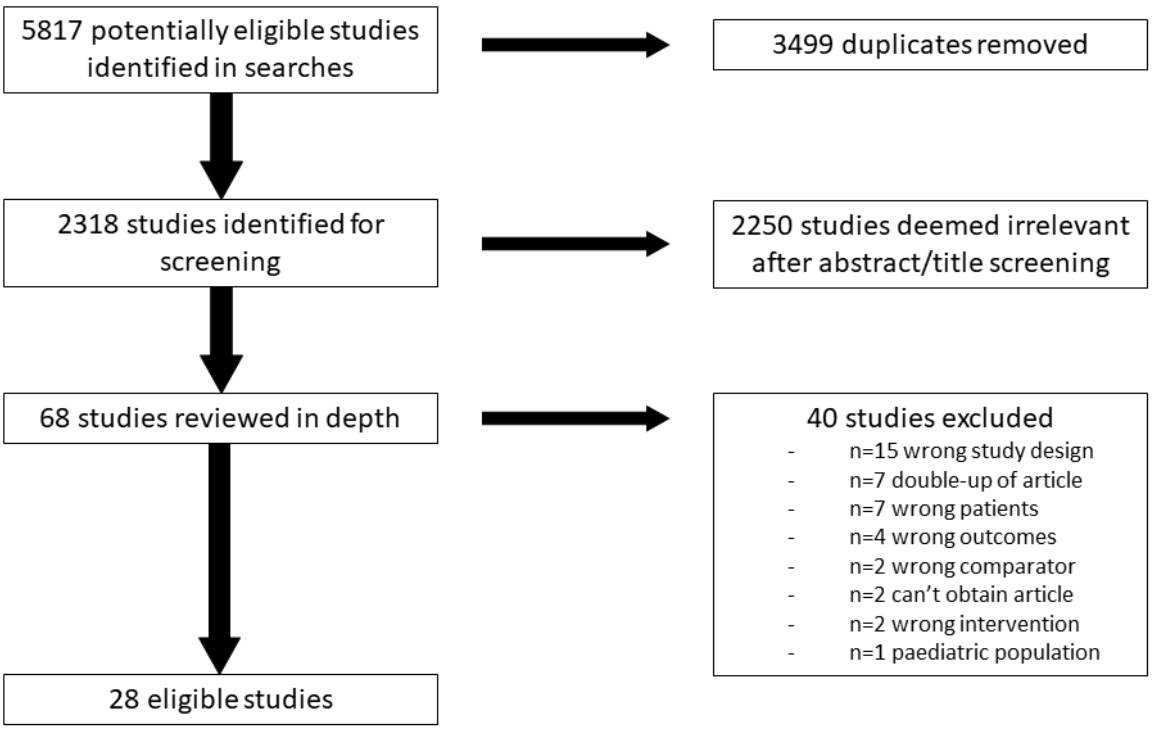


Figure S1. Selection of studies in the review

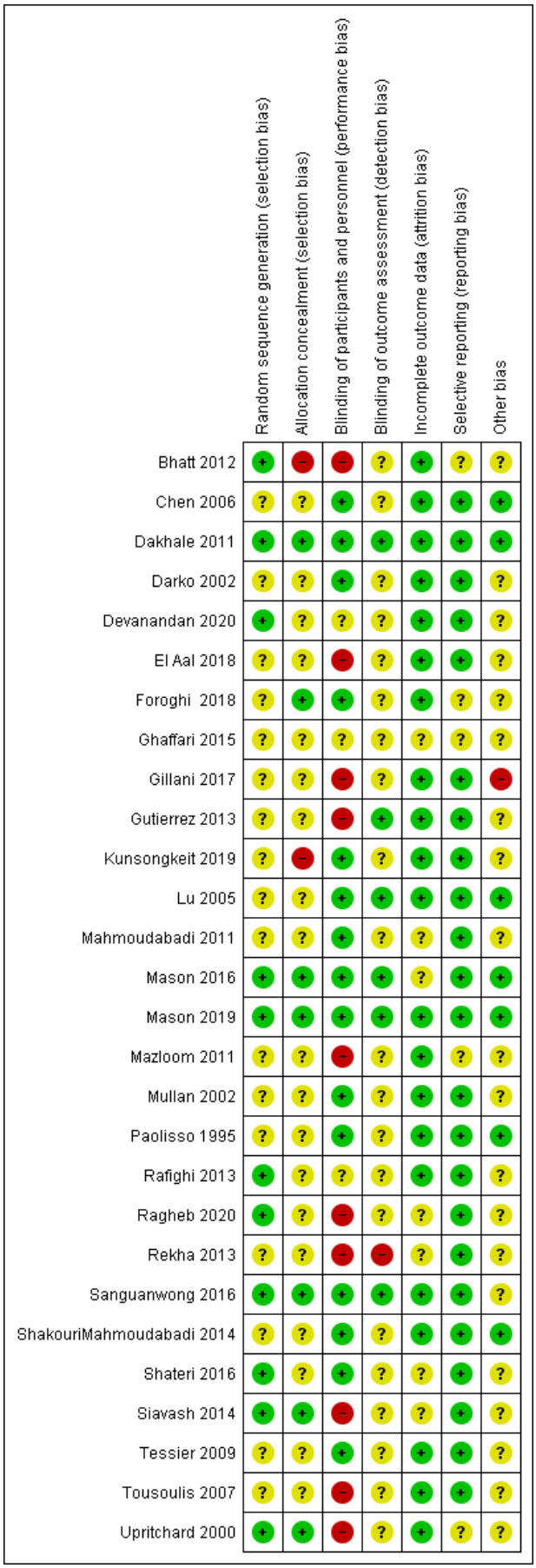
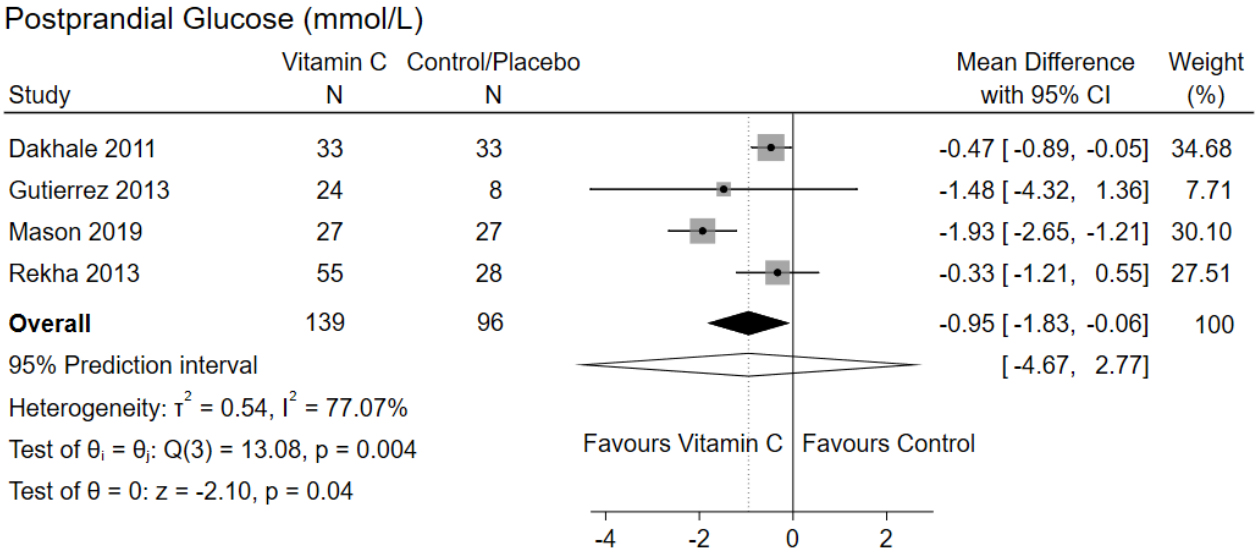
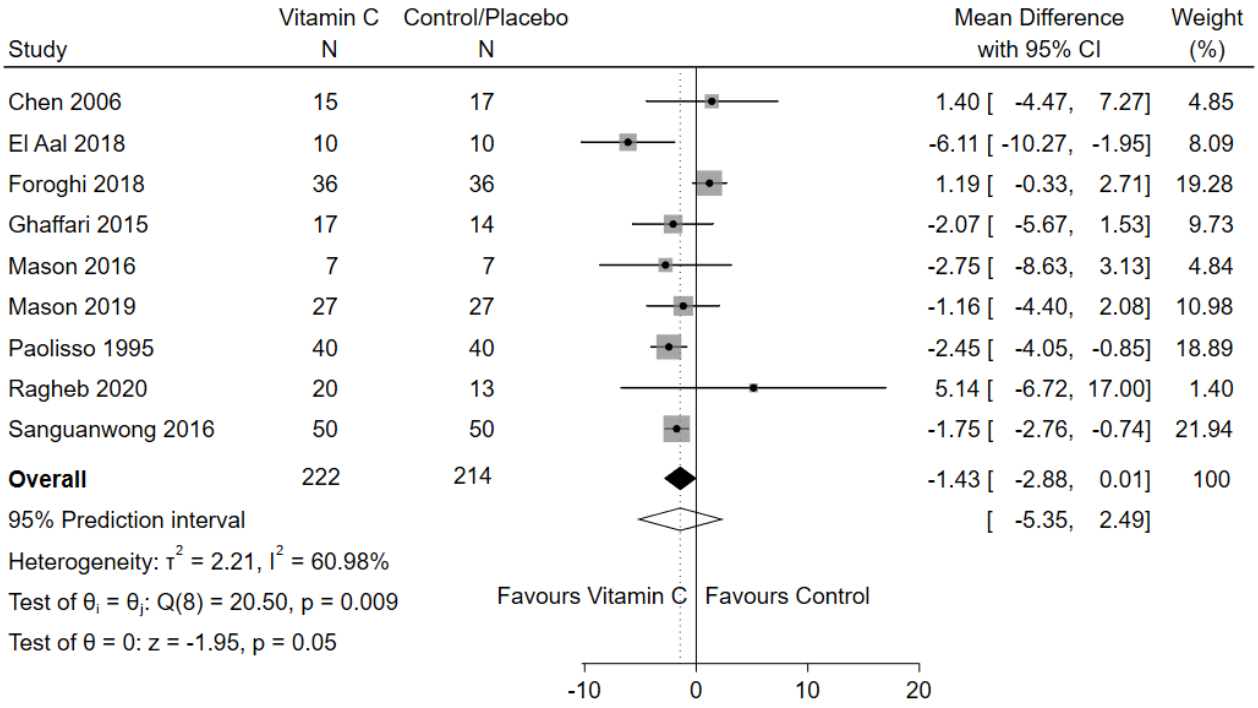


Figure S2. Risk of bias assessment of included studies. Green with a "+" indicates "low risk" of bias; yellow with a "?" indicates "unclear risk" of bias; red with a "-" indicates "high risk" of bias

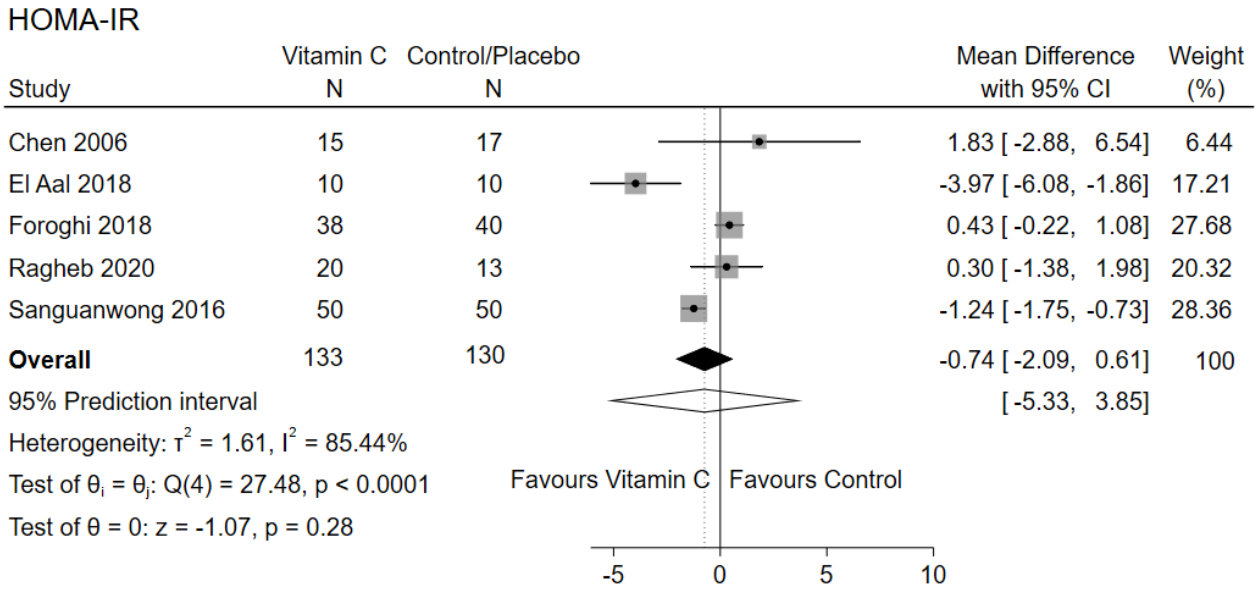
A


Postprandial Glucose (mmol/L)
Study
Vitamin C N
Control/Placebo N
Mean Difference with 95% CI
Weight (%)
Dakhale 2011 33 33 -0.47 [-0.89, -0.05] 34.68
Gutierrez 2013 24 8 -1.48 [-4.32, 1.36] 7.71
Mason 2019 27 27 -1.93 [-2.65, -1.21] 30.10
Rekha 2013 55 28 -0.33 [-1.21, 0.55] 27.51
Overall 139 96 -0.95 [-1.83, -0.06] 100
95% Prediction interval [-4.67, 2.77]
Heterogeneity: τ² = 0.54, I² = 77.07%
Test of θi = θj: Q(3) = 13.08, p = 0.004
Test of θ = 0: z = -2.10, p = 0.04
Favours Vitamin C
Favours Control
-4
-2
0
2

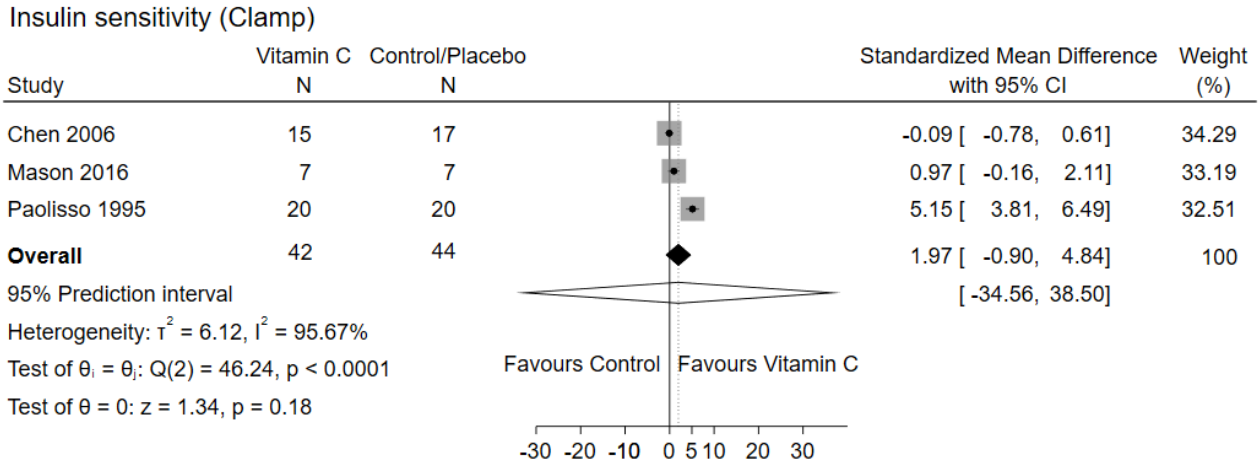
B


Fasting insulin (μU/mL)
Study
Vitamin C N
Control/Placebo N
Mean Difference with 95% CI
Weight (%)
Chen 2006 15 17 1.40 [-4.47, 7.27] 4.85
El Aal 2018 10 10 -6.11 [-10.27, -1.95] 8.09
Foroghi 2018 36 36 1.19 [-0.33, 2.71] 19.28
Ghaffari 2015 17 14 -2.07 [-5.67, 1.53] 9.73
Mason 2016 7 7 -2.75 [-8.63, 3.13] 4.84
Mason 2019 27 27 -1.16 [-4.40, 2.08] 10.98
Paolisso 1995 40 40 -2.45 [-4.05, -0.85] 18.89
Ragheb 2020 20 13 5.14 [-6.72, 17.00] 1.40
Sanguanwong 2016 50 50 -1.75 [-2.76, -0.74] 21.94
Overall 222 214 -1.43 [-2.88, 0.01] 100
95% Prediction interval [-5.35, 2.49]
Heterogeneity: τ² = 2.21, I² = 60.98%
Test of θi = θj: Q(8) = 20.50, p = 0.009
Test of θ = 0: z = -1.95, p = 0.05
Favours Vitamin C
Favours Control
-10
0
10
20

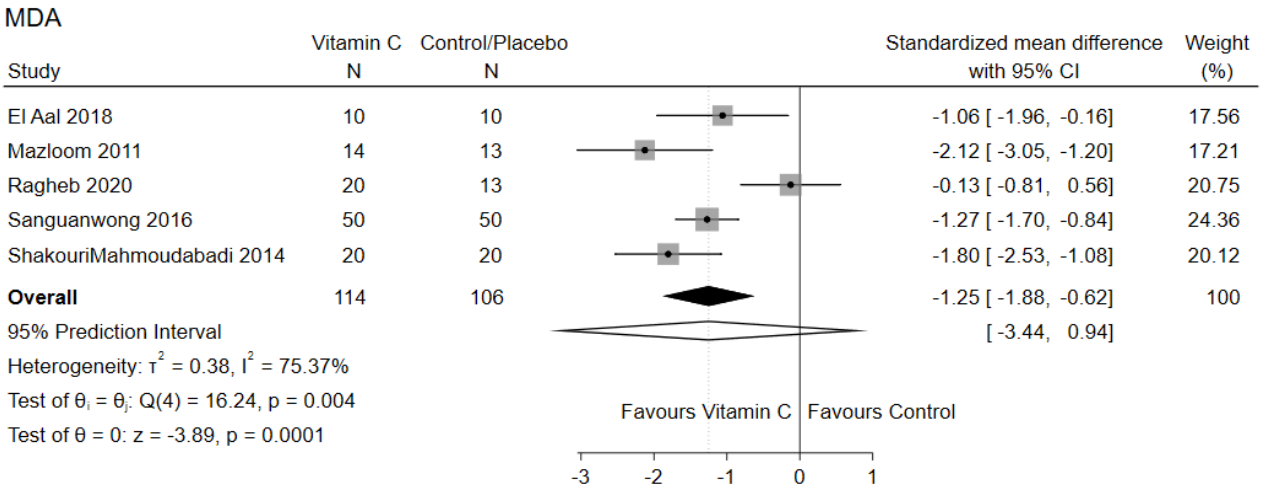
C


HOMA-IR
Study
Vitamin C N
Control/Placebo N
Mean Difference with 95% CI
Weight (%)
Chen 2006 15 17 1.83 [-2.88, 6.54] 6.44
El Aal 2018 10 10 -3.97 [-6.08, -1.86] 17.21
Foroghi 2018 38 40 0.43 [-0.22, 1.08] 27.68
Ragheb 2020 20 13 0.30 [-1.38, 1.98] 20.32
Sanguanwong 2016 50 50 -1.24 [-1.75, -0.73] 28.36
Overall 133 130 -0.74 [-2.09, 0.61] 100
95% Prediction interval [-5.33, 3.85]
Heterogeneity: τ² = 1.61, I² = 85.44%
Test of θi = θj: Q(4) = 27.48, p < 0.0001
Test of θ = 0: z = -1.07, p = 0.28
Favours Vitamin C
Favours Control
-5
0
5
10

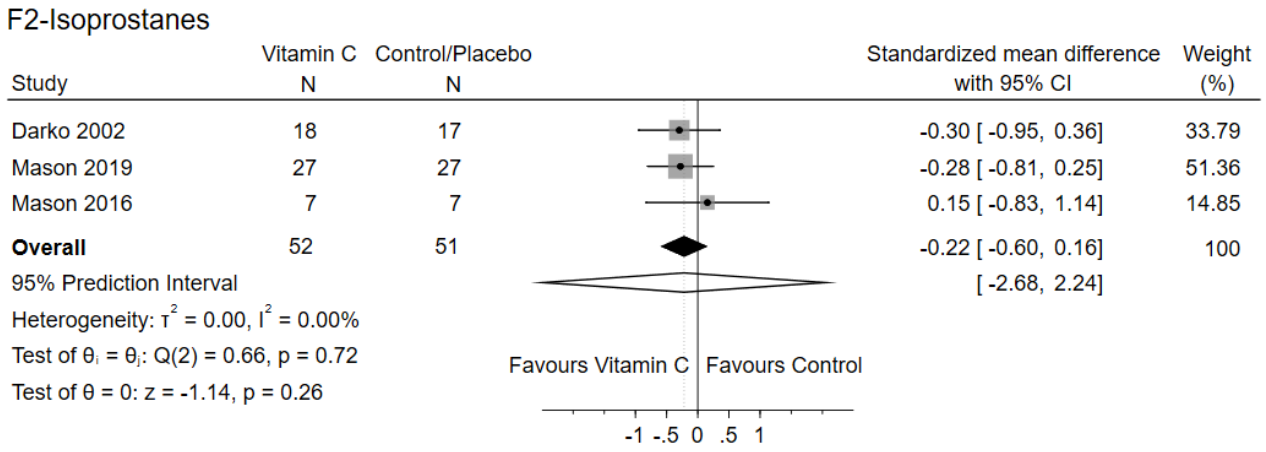
D


Insulin sensitivity (Clamp)
Study
Vitamin C N
Control/Placebo N
Standardized Mean Difference with 95% CI
Weight (%)
Chen 2006 15 17 -0.09 [-0.78, 0.61] 34.29
Mason 2016 7 7 0.97 [-0.16, 2.11] 33.19
Paolisso 1995 20 20 5.15 [3.81, 6.49] 32.51
Overall 42 44 1.97 [-0.90, 4.84] 100
95% Prediction interval [-34.56, 38.50]
Heterogeneity: τ² = 6.12, I² = 95.67%
Test of θi = θj: Q(2) = 46.24, p < 0.0001
Test of θ = 0: z = 1.34, p = 0.18
Favours Control
Favours Vitamin C
-30 -20 -10 0 5 10 20 30

E


MDA
Study
Vitamin C N
Control/Placebo N
Standardized mean difference with 95% CI
Weight (%)
El Aal 2018 10 10 -1.06 [-1.96, -0.16] 17.56
Mazloom 2011 14 13 -2.12 [-3.05, -1.20] 17.21
Ragheb 2020 20 13 -0.13 [-0.81, 0.56] 20.75
Sanguanwong 2016 50 50 -1.27 [-1.70, -0.84] 24.36
ShakouriMahmoudabadi 2014 20 20 -1.80 [-2.53, -1.08] 20.12
Overall 114 106 -1.25 [-1.88, -0.62] 100
95% Prediction Interval [-3.44, 0.94]
Heterogeneity: τ² = 0.38, I² = 75.37%
Test of θi = θj: Q(4) = 16.24, p = 0.004
Test of θ = 0: z = -3.89, p = 0.0001
Favours Vitamin C
Favours Control
-3
-2
-1
0
1

F



G

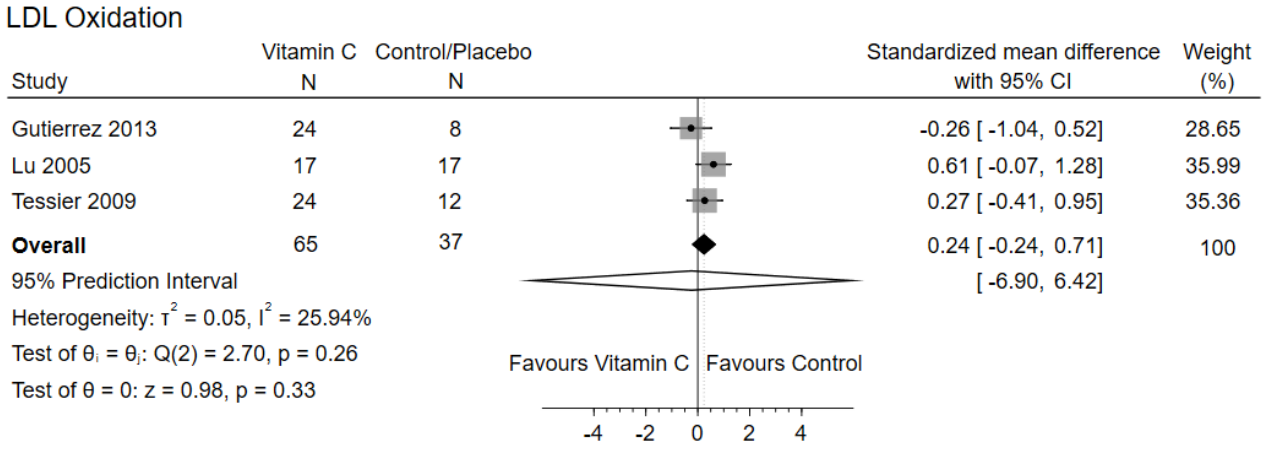
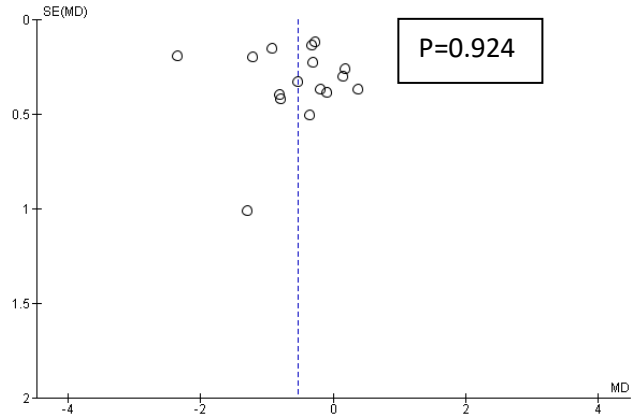
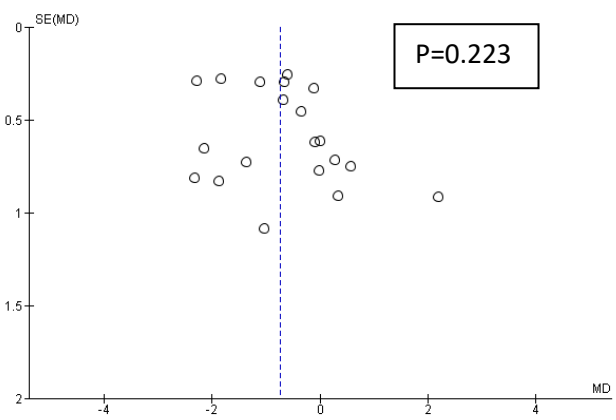


Figure S3. Forest plot of effect of vitamin C supplementation on postprandial glucose (A); fasting insulin (B); homeostasis model assessment of insulin resistance [HOMA-IR] (C); insulin sensitivity [clamp] (D); malondialdehyde (MDA) (E); F_2-Isoprostanes (F); and LDL Oxidation (G).

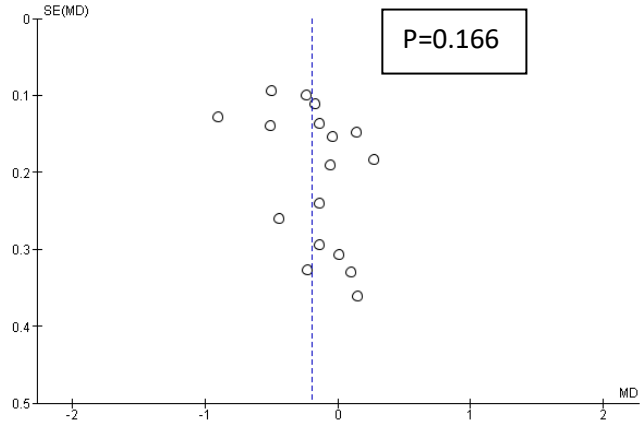
A – HbA1c



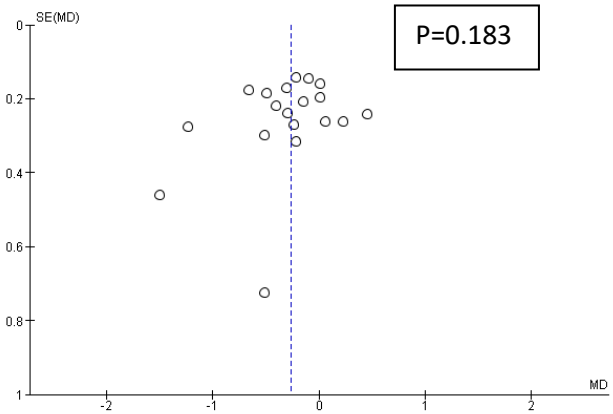
B – Fasting glucose



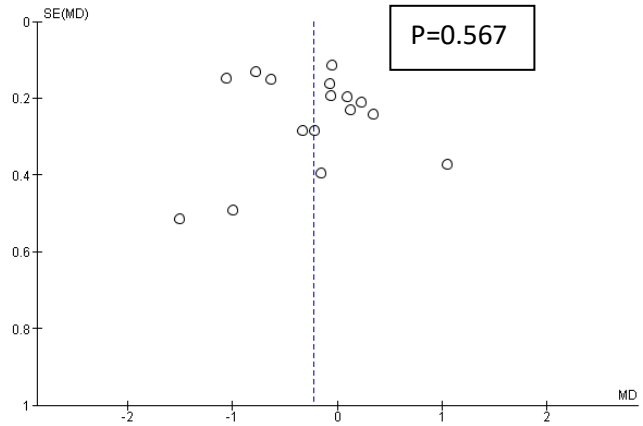
C – Triglycerides



D – Total Cholesterol



E – LDL Cholesterol



F – HDL Cholesterol

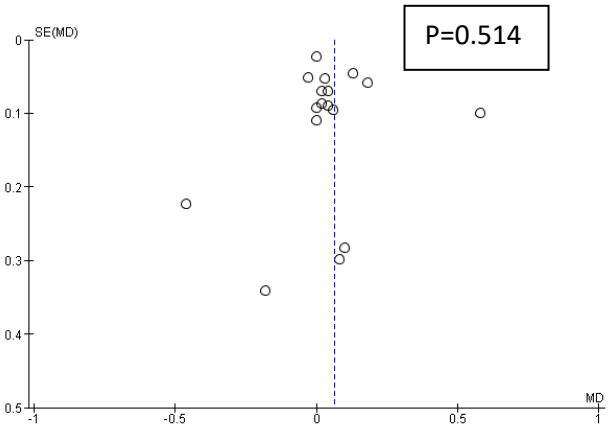


Figure S4. Publication bias funnel plots and Egger Regression significance values for outcomes with at least 10 studies and 1 medium/large size study included: HbA1c (A); fasting glucose (B); triglycerides (C); total cholesterol (D); LDL cholesterol (E); and HDL cholesterol (F).