Online Supplementary Material

Figure S1: Incidence of Hypertension

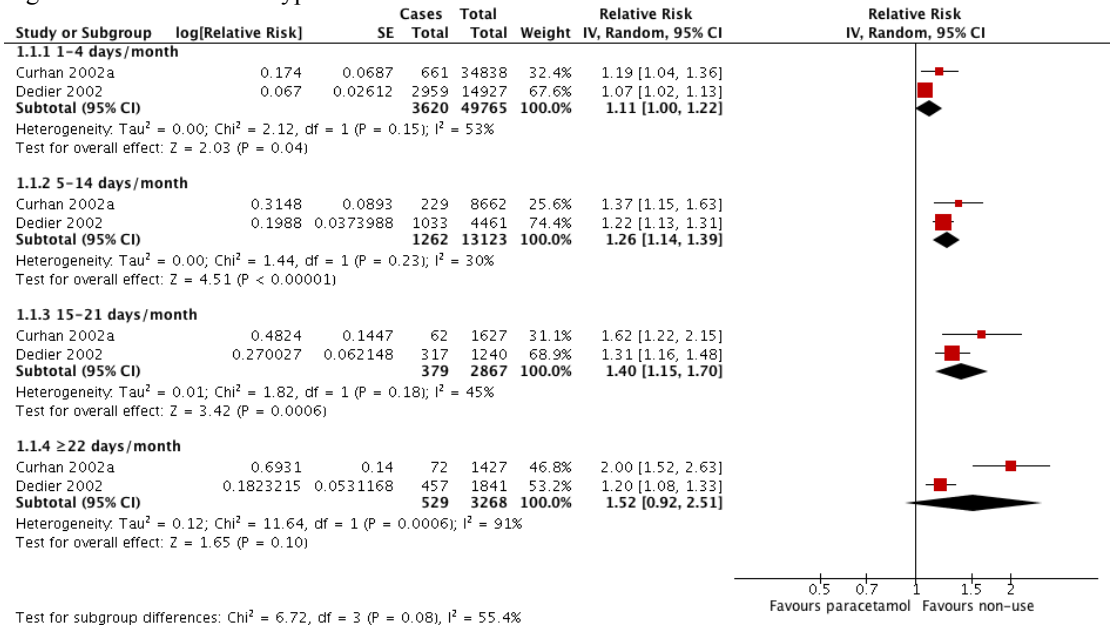


Figure S2: Incidence of Myocardial Infarction

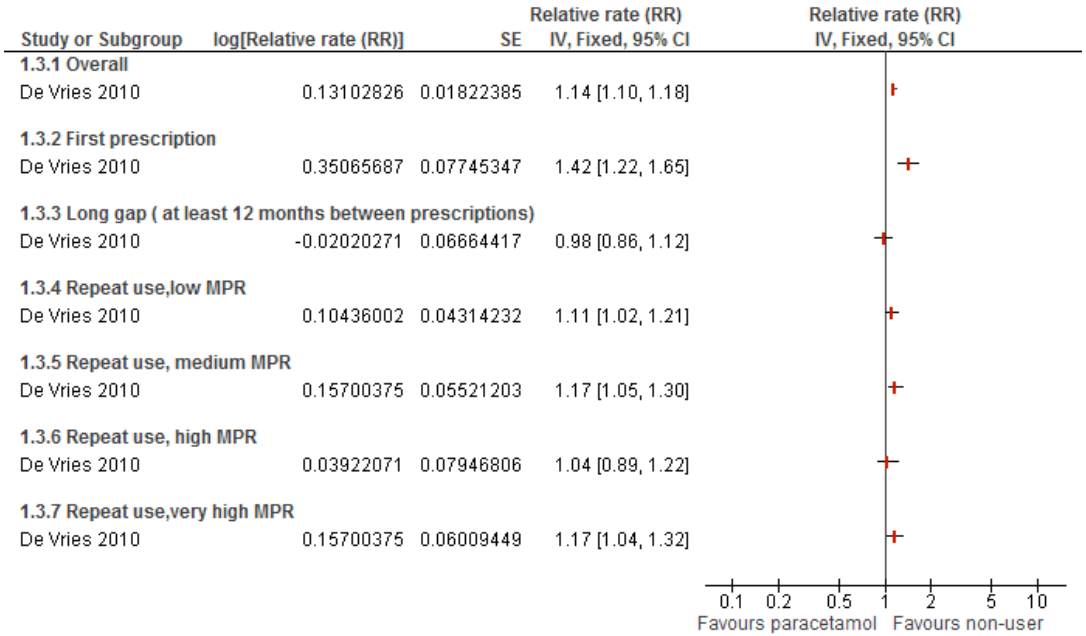


Figure S3: Incidence of Stroke

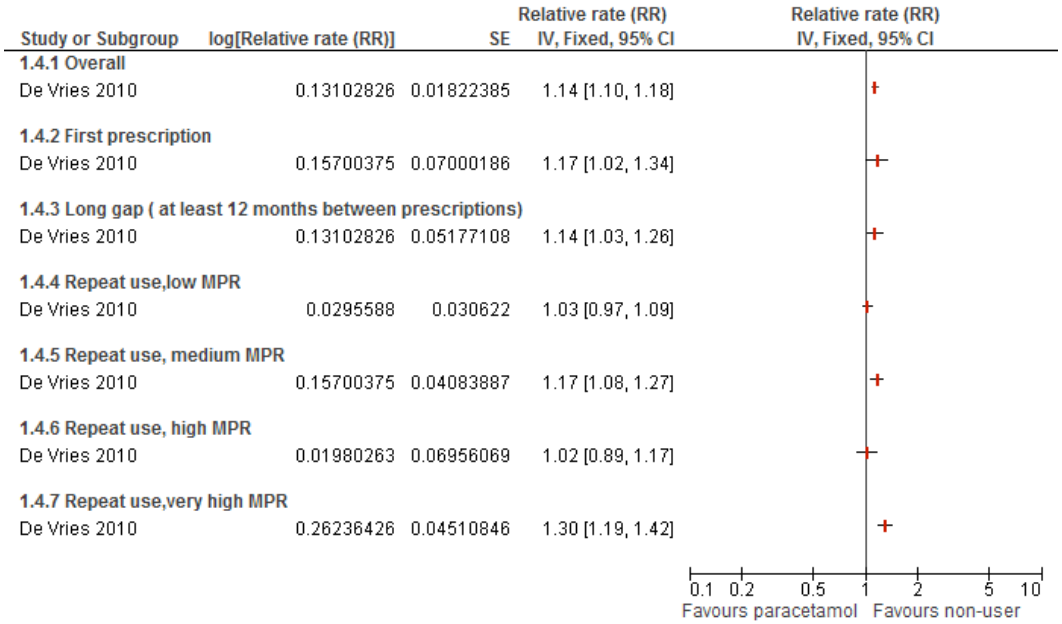


Figure S4: Incidence of acute renal failure

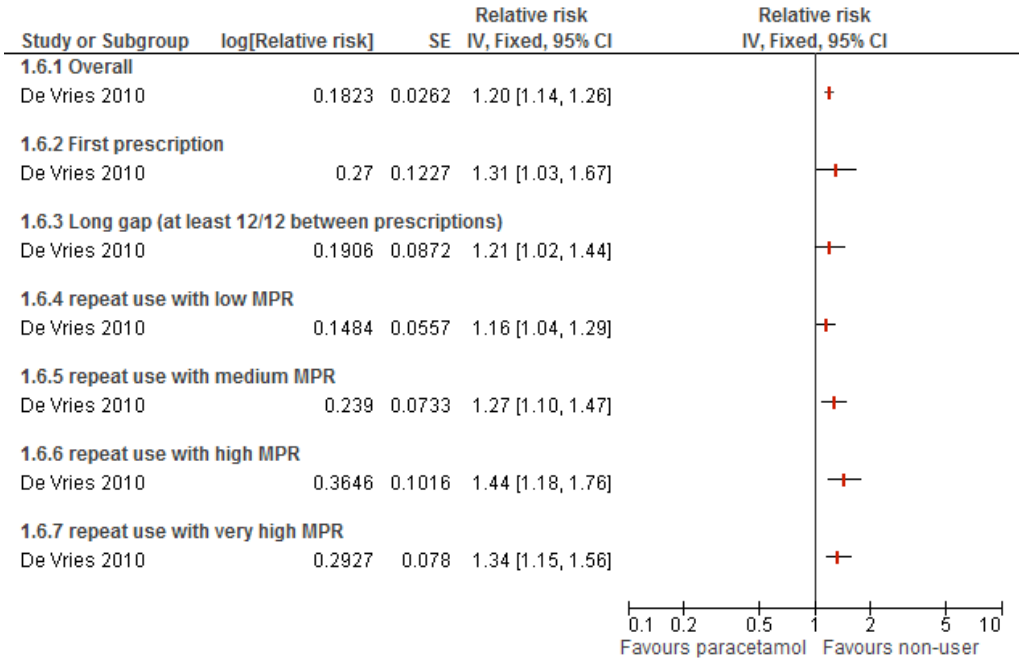
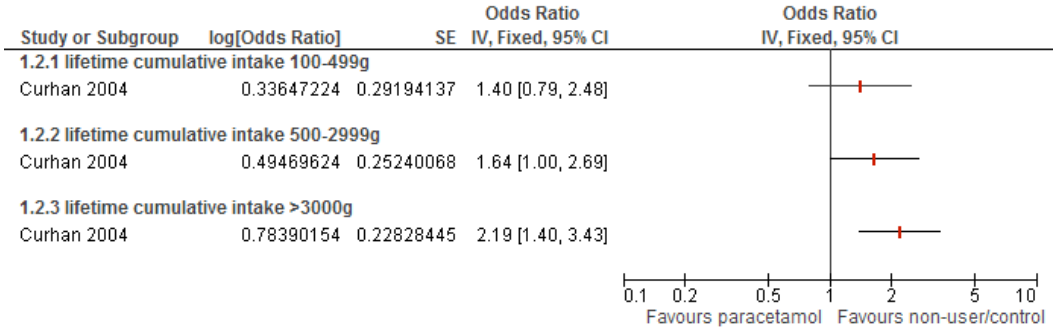


Figure S5: ≥ 30% decrease in eGFR



eFigure 6: Increased creatinine concentration of ≥ 0.3 mg/dL

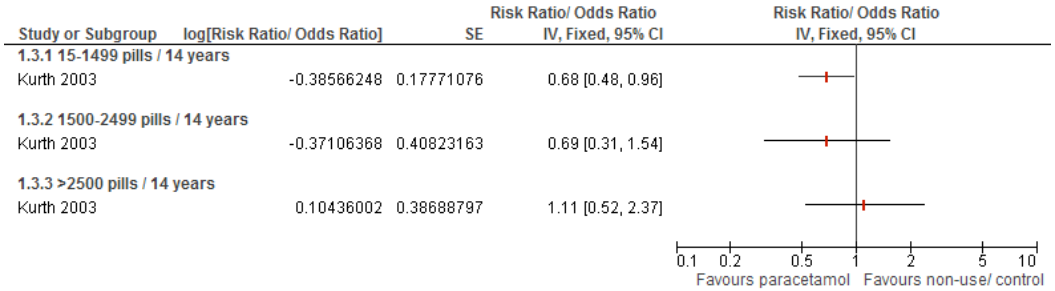


Figure S7: Differences in estimated progression rates, (change in eGFR in m L/min/1.73 m^2 per year)

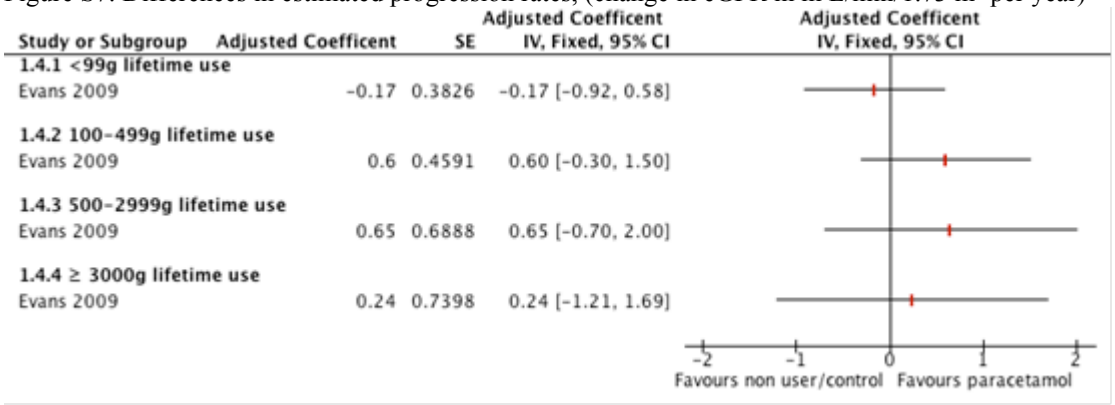


Figure S8: Time to renal replacement therapy

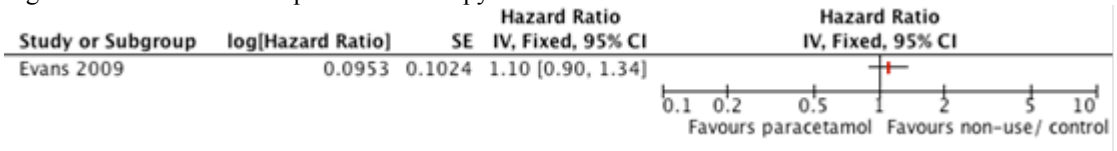


Figure S9: Search Strategies: Observational studies search terms: Medline search terms: Searched on the OVID interface

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/

4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Figure S10: Search Strategies: Observational studies search terms: Embase search terms: Searched on the OVID interface

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.

16.	or/1-8,11-15

Figure S11: Search Strategies Event Search Terms: Medline search terms: searched on the OVID interface

1.	exp acetaminophen/
2.	(paracetamol or acetaminophen or panadol or tylenol or acetominophen or acamol or acephen).ti,ab.
3.	or/1-2
4.	(ae or co or de or po or to).fs.
5.	(side effect* or (adverse adj2 (effect* or event*)) or safety or tolerability or toxicity).ti,ab.
6.	((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab.
7.	or/4-6
8.	3 and 7

Figure S12: Search Strategies Event Search Terms: Embase search terms: Searched on the OVID interface

1.	exp paracetamol/
2.	(paracetamol or acetaminophen or panadol or tylenol or acetominophen or acamol or acephen).ti,ab.
3.	or/1-2
4.	(side effect* or (adverse adj2 (effect* or event*)) or safety or tolerability or toxicity).ti,ab.
5.	((adverse or undesirable or harm* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab.
6.	(ae or si or to or co).fs.
7.	or/4-6
8.	3 and 7

Table S1: Studies included in the review. USA – United States of America, UK – United Kingdom, CKD – Chronic Kidney Disease, AE – Adverse Event, MI- Myocardial Infarction, EtOH – Ethanol, BMI – Body Mass Index, GI - Gastrointestinal, TIA – Transient Ischaemic Attack, IBD – Inflammatory Bowel Disease, ACEi – Angiotenisn converting enzyme inhibitor, ARB –Angiotenisn receptor blocker, HDL – High Density Lipoprotein, eGFR – Estimated Glomerular Filtration Rate.

Study Name	Study Site	Study Design	N	Duration of follow up (maximum)	Participants	Confounders adjusted for:	Measure of effect	Outcomes	Exposure (no-use versus:)	Results
Chan 2006 [10]	USA	Cohort	70,971	12 years	Female registered nurses aged 30-55 years	Age, parental history of MI before aged 60 years, history of diabetes, history of hypercholesterolemia, smoking history, BMI, regular moderate or vigorous exercise, postmenopausal hormone use, current multivitamin use, energy adjusted quintiles of folate, omega-3- fatty acids, saturated fats, other analgesic use, history of hypertension.	Risk Ratio	Cardiovascular AEs (confirmed or probable non –fatal myocardial infarction, non-fatal stroke. Fatal coronary heart disease or fatal stroke)	1-4 days/month use 5-14 days/month use 15-21 days/month use >22 days/month use 1 day/week use 2-3 days/week use 4-5 days/week use ≥ 6 days/week use 1-2 tablets/week 3-5 tablets/week 6-14 tablets/week ≥ 15 tablets/week	0·98 (0·84–1·14) 1·09 (0·91–1·30) 1·22 (0·95–1·56) 1·35 (1·14–1·59) 0·94 (0·62–1·44) 1·28 (0·94–1·75) 1·49 (0·99–2·24) 1·50 (1·10–2·04) 1·19 (0·81-1·76) 1·16 (0·76-1·76) 1·47 (1·06-2·03) 1·68 (1·10-2·58)
Curhan 2002 [11]	USA	Cohort	80,020	2 years	Female registered nurses aged 30-55 years	Age, BMI, intake of EtOH and sodium, family history of hypertension, oral contraceptive pill use, category of use of the other individual analgesics.	Relative Risk	Incidence of hypertension	1-4 days/month use 5-14 days/month use 15-21 days/month use >22 days/month use	1·19 (1·04-1·36) 1·37 (1·15-1·64) 1·62 (1·22-2·16) 2·00 (1·52-2·62)
Dedier 2002 [12]	USA	Cohort	57,935	2 years	Female registered nurses aged 30-55 years	Age, BMI, intake of sodium and alcohol, physical activity, family history of hypertension, history of diabetes, and smoking.	Relative Risk	Incidence of hypertension	1-4 days/month use 5-14 days/month use 15-21 days/month use >22 days/month use	1·07 (1·02-1·13) 1·22 (1·14-1·32) 1·31 (1·16-1·48) 1·20 (1·08-1·33)
Curhan 2004[13]	USA	Cohort	1,697	11 years	Female registered nurses aged 30-55 years	Age, weight, history of hypertension, systolic and diastolic blood pressure, history of diabetes, current smoker, lifetime consumption of all analgesics.	Odds Ratio	Decrease in eGFR of at least 30 mL/min/1.73m^2	100-499g lifetime intake 500-2999g lifetime intake >3000g lifetime intake	1·80 (1·02-3·17) 2·23 (1·36-3·63) 2·04 (1·28-3·24)
								≥ 30% decrease in eGFR	100-499g lifetime intake 500-2999g lifetime intake >3000g lifetime intake	1·40 (0·79-2·49) 1·64 (1·00-2·69) 2·19 (1·40-3·45)
De Vries 2010 [8]	UK	Cohort	382,404	20 years	Patients aged ≥ 18 received a prescription for paracetamol or ibuprofen	Standard Set: Age, gender, BMI, Calendar Year, smoking history, EtOH use, number of visits to general practitioner in previous 12 months, hospital admission in previous year, socioeconomic status in location of practice,	Relative Rate	-	Differing medication possession ratios (MPR): The MPR is defined as the ratio of duration of the previous prescription, to the time between that prescription and the current prescription. Low MPR equal to < 0.40, medium MPR 0.40–0.59, high MPR 0.60–0.79 and very high	

De Vries 2010 [8]	UK	Cohort	382,404	20 years	Patients aged ≥ 18 received a prescription for paracetamol or ibuprofen	Standard Set: Age, gender, BMI, Calendar Year, smoking history, EtOH use, number of visits to general practitioner in previous 12 months, hospital admission in previous year, socioeconomic status in location of practice,	Relative Rate	-	Differing medication possession ratios (MPR): The MPR is defined as the ratio of duration of the previous prescription, to the time between that prescription and the current prescription. Low MPR equal to < 0.40, medium MPR 0.40–0.59, high MPR 0.60–0.79 and very high MPR equal to > 0.8	
						Standard Set plus: Upper GI events, osteoarthritis, rheumatoid arthritis, ischemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes mellitus, hyperthyroidism, stroke or TIA, cancer (excluding non-melanoma skin cancer), IBD, autoimmune disease, depression, drug abuse, prescriptions in the last six months of anticoagulants, oral glucocorticoids, diuretics, cardiac glycosides, statins, angiotensin receptor blockers, hypnotics and anxiolytics, antipsychotic drugs, antibacterial drugs, aminosalicylates, antidepressants)		All-cause mortality	First prescription Long gap (patients with at least 12 months between prescriptions) Low MPR Medium MPR High MPR Very High MPR	1·95 (1·87-2·04) 1·18 (1·14-1·23) 0·95 (0·92-0·97) 1·08 (1·05-1·12) 1·27 (1·21-1·33) 1·63 (1·58-1·68)
						Standard Set plus: history of ischemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes mellitus. hyperthyroidism, hyperlipidemia, prior prescribing of diuretics, cardiac glycosides, statins, angiotensin receptor		Incidence of myocardial infarction	First prescription Long gap (patients with at least 12 months between prescriptions) Low MPR Medium MPR High MPR	1·42 (1·22-1·65) 0·98 (0·86-1·11) 1·11 (1·02-1·19) 1·17 (1·05-1·29) 1·04 (0·89-1·23) 1·17 (1·04-1·32)

						Standard set plus: history of stroke or transient ischemic attack, history heart failure, hypertension, cerebrovascular disease, diabetes mellitus. hyperthyroidism, hyperlipidemia, prior prescribing of diuretics, cardiac glycosides, statins, angiotensin receptor blockers or oral glucocorticoids		Incidence of Stroke	First prescription Long gap (patients with at least 12 months between prescriptions) Low MPR Medium MPR High MPR Very High MPR	1·17 (1·02-1·35) 1·14 (1·03-1·25) 1·03 (0·97-1·10) 1·17 (1·08-1·27) 1·02 (0·89-1·15) 1·30 (1·19-1·41)
						Standard Set plus: history of upper GI events, osteoarthritis or rheumatoid arthritis, prior prescription of anticoagulants, aspirin, oral corticosteroids, proton pump inhibitors H2 receptor antagonists.		Upper GI AEs (gastroduodenal ulcers and complications such as upper GI haemorrhages)	First prescription Long gap (patients with at least 12 months between prescriptions) Low MPR Medium MPR High MPR Very High MPR	1·74 (1·53-1·59) 1·30 (1·17-1·46) 1·11 (1·04-1·21) 1·25 (1·12-1·38) 1·49 (1·29-1·71) 1·49 (1·34-1·66)
						Standard set plus: history of cancer (excluding non-melanoma skin cancer), congestive heart failure, inflammatory bowel disease, autoimmune disease, diabetes mellitus, hypertension, prior prescription of hypnotics or anxiolytics, antipsychotics, antibacterial agents, aminosalycylates or oral glucocorticoids		Incidence of acute renal failure	First prescription Long gap (patients with at least 12 months between prescriptions) Low MPR Medium MPR High MPR Very High MPR	1·31 (1·03-1·68) 1·21 (1·02-1·43) 1·16 (1·04-1·29) 1·27 (1·10-1·47) 1·44 (1·18-1·75) 1·34(1·15-1·57)
Evans 2009 [14]	Swede n	Cohort	801	7 years	People diagnosed with incident CKD aged ≥ 18	Gender, age, ACEi or ARB use, mean arterial pressure at baseline	Regression Coefficient	Differences in estimated progression rates, (change in eGFR in mL/min/1.73 m2 per year)	<99g lifetime intake 100-499g lifetime intake 500-2999g lifetime intake >3000g lifetime intake	-0·17 (-0·9-0·6) 0·60 (-0·3-1·5) 0·65(-0·7 -2·0) 0·24 (-1·2-1·7)
						Gender, high level of proteinuria, high means arterial pressure at baseline, diabetic nephropathy.	Hazard Ratio	Time to renal replacement therapy	Regular use (at least twice a week for two months prior to inclusion)	1·1 (0·9-1·4)

Kurth 2003 [15]	USA	Cohort	22,071	14 years	Healthy male physicians	Age, BMI, history of hypertension, history of self-reported diabetes, physical activity, family history of MI, smoking status, HDL level baseline creatinine level, randomized beta carotene assignment, total analgesic use.	Odds Ratio	Increased creatinine concentration of ≥ 0.3 mg/dL	12-1499 pills/14 years 1500-2499 pills/14 years >2500 pills/14 years	0·68(0·48-0·98) 0·69(0·31-1·54) 1·11(0·52-2·37)
								Decrease in eGFR of at least 30 mL/min/1.73m^2	12-1499 pills/14 years 1500-2499 pills/14 years >2500 pills/14 years	0·53(0·36-0·78) 0·65(0·29-1·45) 1·28(0·61-2·69)
Lipworth 2003 [9]	Denmark	Cohort	49,890	7 years	People prescribed paracetamol aged over 16	Nil	Standardised mortality ratio	All-cause mortality	Prescribed paracetamol during lifetime	1·9 (1·88-1·94)
								Renal Failure		1·8 (1·3-2·5)
								Ischemic Heart disease		1·6 (1·5-1·6)
								Other heart disease		1·6 (1·5-1·8)
								Cerebrovascular disease		1·6 (1·5-1·7)

Table S2: Mortality: GRADE Clinical evidence profile: Mortality: Paracetamol use versus non-use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paracetamol**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality – Overall (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	no serious imprecision	none	-	-	RR 1.28 (1.26 to 1.3)	-	VERY LOW	IMPORTANT
Mortality - First prescription (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	no serious imprecision	none	-	-	RR 1.95 (1.87 to 2.03)	-	VERY LOW	IMPORTANT
Mortality - Long gap (at least 12 months between prescriptions) (De Vries 2010)												
1	observational	Serious[1]	no serious	None	no serious	none	-	-	RR 1.18 (1.14 to	-		IMPORTANT

	study		inconsistency		imprecision				1.22)		VERY LOW	
Mortality - repeat use with low MPR (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	no serious imprecision	none	-	-	RR 0.95 (0.92 to 0.98)	-	VERY LOW	IMPORTANT
Mortality - repeat use with medium MPR (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	no serious imprecision	none	-	-	RR 1.08 (1.05 to 1.11)	-	VERY LOW	IMPORTANT
Mortality - repeat use with high MPR (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	Serious[2]	none	-	-	RR 1.27 (1.21 to 1.33)	-	VERY LOW	IMPORTANT
Mortality - repeat use with very high MPR (De Vries 2010)												
1	observational study	Serious[1]	no serious inconsistency	None	no serious imprecision	none	-	-	RR 1.63 (1.58 to 1.68)	-	VERY LOW	IMPORTANT

1 Unclear whether DeVries (2010) accounted for all essential confounders identified by the GDG, study reported relative risks and prevalence could not be calculated.

2 Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in one direction making the effect size uncertain

Table S3 GRADE clinical evidence profile: Cardiovascular adverse events: Paracetamol use versus non-use

Quality assessment						No of patients	Effect	Quality	Importanc

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Cardiovascular adverse events - 1-4 days per month use (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	None		3.63%	RR 0.95 (0.79 to 1.14)	2 fewer per 1000 (from 8 fewer to 5 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - 5-14 days per month use(Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	None		3.63%	RR 1 (0.81 to 1.23)	0 fewer per 1000 (from 7 fewer to 8 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events – 15-21 days per month use(Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	serious[3]	serious[4]	None		3.63%	RR 0.91 (0.67 to 1.24)	3 fewer per 1000 (from 12 fewer to 9 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - >22 days per month use (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	no serious imprecision	None		3.63%	RR 1.44 (1.27 to 1.63)	16 more per 1000 (from 10 more to 23 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - Taking tablets on 1 day/ week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	very serious[5]	None		3.63%	RR 0.94 (0.62 to 1.43)	2 fewer per 1000 (from 14 fewer to 16 more)	VERY LOW	IMPORTAN

Quality assessment							No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Cardiovascular adverse events - Taking tablets on 2-3 day/ week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	serious[4]	none		3.63%	RR 1.23 (0.94 to 1.61)	8 more per 1000 (from 2 fewer to 22 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - Taking tablets on 4-5 day/ week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	very serious[5]	none		3.63%	RR 1.49 (0.99 to 2.24)	18 more per 1000 (from 0 fewer to 45 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - Taking tablets on >6 day/ week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	serious[4]	none		3.63%	RR 1.5 (1.1 to 2.05)	18 more per 1000 (from 4 more to 38 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - 1-2 tablets per week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	serious[4]	none		3.63%	RR 1.19 (0.81 to 1.75)	7 more per 1000 (from 7 fewer to 27 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - 3-5 tablets per week (Chan 2006)												
1	observational	serious[1,2]	no serious	none	serious[4]	none		3.63%	RR 1.16 (0.76	6 more per 1000 (from		IMPORTAN

Quality assessment							No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
	study		inconsistency						to 1.77)	9 fewer to 28 more)	VERY LOW	
Cardiovascular adverse events - 6-14 tablets per week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	serious[4]	none		3.63%	RR 1.47 (1.06 to 2.04)	17 more per 1000 (from 2 more to 38 more)	VERY LOW	IMPORTAN
Cardiovascular adverse events - >15 tablets per week (Chan 2006)												
1	observational study	serious[1,2]	no serious inconsistency	none	serious[4]	none		3.63%	RR 1.68 (1.1 to 2.57)	25 more per 1000 (from 4 more to 57 more)	VERY LOW	IMPORTAN
Myocardial Infarction – Overall (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.14 (1.1 to 1.18)	-	VERY LOW	IMPORTAN
Myocardial Infarction - First prescription (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.42 (1.22 to 1.65)	-	VERY LOW	IMPORTAN
Myocardial Infarction - Long gap (at least 12 months between prescriptions) (relative rate) (DeVries 2010)												

Quality assessment							No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 0.98 (0.86 to 1.12)	-	VERY LOW	IMPORTAN
Myocardial Infarction - Repeat use, low MPR [1] (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 1.11 (1.02 to 1.21)	-	VERY LOW	IMPORTAN
Myocardial Infarction - Repeat use, medium MPR (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.17 (1.05 to 1.3)	-	VERY LOW	IMPORTAN
Myocardial Infarction - Repeat use, high MPR (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 1.04 (0.89 to 1.22)	-	VERY LOW	IMPORTAN
Myocardial Infarction - Repeat use, very high MPR (relative rate) (DeVries 2010)												
1	observational	serious[2,6,]	no serious	none	serious[4]	none	-	-	RR 1.17 (1.04	-		IMPORTAN

[1] Medication possession ratio

Quality assessment							No of patients		Effect		Quality	Importanc
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paracetamol**	**Control**	**Relative (95% CI)**	**Absolute**		
	study	[3]	inconsistency						to 1.32)		VERY LOW	
Stroke – Overall (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 1.14 (1.1 to 1.18)	-	VERY LOW	IMPORTAN
Stroke - First prescription (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.17 (1.02 to 1.34)	-	VERY LOW	IMPORTAN
Stroke - Long gap (relative rate) (at least 12 months between prescriptions) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.14 (1.03 to 1.26)	-	VERY LOW	IMPORTAN
Stroke - Repeat use, low MPR(relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 1.03 (0.97 to 1.09)	-	VERY LOW	IMPORTAN
Stroke - Repeat use, medium MPR (relative rate) (DeVries 2010)												

Quality assessment							No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.17 (1.08 to 1.27)	-	VERY LOW	IMPORTAN
Stroke - Repeat use, high MPR (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	no serious imprecision	none	-	-	RR 1.02 (0.89 to 1.17)	-	VERY LOW	IMPORTAN
Stroke - Repeat use, very high MPR (relative rate) (DeVries 2010)												
1	observational study	serious[2,6,3]	no serious inconsistency	none	serious[4]	none	-	-	RR 1.3 (1.19 to 1.42)	-	VERY LOW	IMPORTAN

1 Chan (2006) did not pre-specify that they would report all events as cardiovascular events
2 The study did not report Hazard Ratios
3 Unclear whether DeVries 2010 accounts for other analgesic use as confounder
4 Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in one direction making the effect size uncertain
5 Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in both directions making the effect size very uncertain
6 Cannot calculate prevalence for DeVries 2010

Table S4: GRADE Clinical evidence profile: Upper GI adverse events: Paracetamol use vs. non-use

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paracetamol**	**Control**	**Relative (95% CI)**	**Absolute**		
GI AE or Bleed - Overall paracetamol users vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	no serious imprecision	None	-		RR 1.36 (1.31 to 1.41)	-	VERY LOW	IMPORTANT
GI AE or Bleed - First prescription vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	no serious imprecision	None	-		RR 1.74 (1.53 to 1.98)	-	VERY LOW	IMPORTANT
GI AE or Bleed - long gap (12 months between prescription) vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	Serious[4]	None	-		RR 1.3 (1.17 to 1.44)	-	VERY LOW	IMPORTANT
GI AE or Bleed - repeat use, low MPR vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	no serious imprecision	None	-		RR 1.11 (1.04 to 1.18)	-	VERY LOW	IMPORTANT
GI AE or Bleed - repeat use, medium MPR vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	Serious[4]	None	-		RR 1.25 (1.12 to 1.4)	-	VERY LOW	IMPORTANT
GI AE or Bleed - repeat use, high MPR vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	no serious imprecision	None	-		RR 1.49 (1.29 to 1.72)	-	VERY LOW	IMPORTANT
GI AE or Bleed - repeat use, very high MPR vs non-use (relative rate) (De Vries 2010)												
1	observational study	serious[2,3,1]	no serious inconsistency	None	no serious imprecision	None	-		RR 1.49 (1.34, 1.66)	-	VERY LOW	IMPORTANT

1 Unclear whether DeVries (2010) accounted for all NSAID use
2 The study did not report Hazard Ratios
3 Prevalence could not be calculated for the study
4 Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in one direction making the effect size uncertain

Table S5: GRADE clinical evidence profile: Incidence of hypertension: Paracetamol use vs. non-use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Incidence of hypertension- frequency of use - 1-4 days/month (Curhan 2002, Dedier 2002)												
2	observational studies	serious[1,2]	Serious[3]	none	Serious[4]	None			RR 1.11 (1.00 to 1.22)	10 more per 1000 (from 0 more to 20 more)	VERY LOW	IMPORTANT
Incidence of hypertension- frequency of use - 5-14 days/month (Curhan 2002, Dedier 2002)												
2	observational studies	serious[1,2]	no serious inconsistency	none	Serious[4]	None			RR 1.26 (1.14 to 1.39)	23 more per 1000 (from 13 more to 23 more)	VERY LOW	IMPORTANT
Incidence of hypertension- frequency of use - 15-21 days/month (Curhan 2002, Dedier 2002)												
2	observational studies	serious[1,2]	no serious inconsistency	none	Serious[4]	None			RR 1.40 (1.15 to 1.70)	34 more per 1000 (from14 more to 53 more)	VERY LOW	IMPORTANT
Incidence of hypertension- frequency of use - >22 days/month (Curhan 2002, Dedier 2002)												
2	observational studies	serious[1,2]	Very serious[3]	none	no serious imprecision	none			RR 1.52 (0.92 to 2.531)	142 more per 1000 (from 8 fewer to 92 more)	VERY LOW	IMPORTANT

1 The studies did not account for all confounders
2 The study did not report Hazard Ratios
3 Outcomes were downgraded by one increment if the degree of inconsistency across studies was deemed serious (I squared 50 - 74%, or chi square p value of 0.05 or less). Outcomes were downgraded by two increments if the degree of inconsistency was deemed very serious (I squared 75% or more. Inconsistent outcomes were therefore re-

analysed using a random effects model, rather than the default fixed effect model used initially for all outcomes. The point estimate and 95% CIs given in the grade table and forest plots are those derived from the new random effects analysis.
4 Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in one direction making the effect size uncertain

Table S6: GRADE clinical evidence profile: Renal adverse events: Paracetamol use versus non-use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Decrease in eGFR of at least 29-30 mL/min - cumulative pills/ 14 years: 12-1499 pills (Kurth 2003)												
1	observational study	serious[1]	no serious inconsistency	serious	serious[3]	None	-	-	OR 0.53 (0.36 to 0.78)	-	VERY LOW	IMPORTANT
Decrease in eGFR of at least 29-30 mL/min - cumulative pills/ 14 years: 1500-2499 pills (Kurth 2003)												
1	observational study	serious[1]	no serious inconsistency	serious	very serious[4]	None	-	-	OR 0.65 (0.29 to 1.46)	-	VERY LOW	IMPORTANT
Decrease in eGFR of at least 29-30 mL/min - cumulative pills/ 14 years: >2500 pills (Kurth 2003)												
1	observational study	serious[1]	no serious inconsistency	serious	very serious[4]	None	-	-	OR 1.28 (0.61 to 2.69)	-	VERY LOW	IMPORTANT
Decrease in eGFR of at least 29-30 mL/min - lifetime cumulative intake: 100-499g (Curhan 2004)												
1	observational study	serious[5]	no serious inconsistency	serious	serious[3]	none	-	6.84%	OR 1.8 (1.02 to 3.18)	48 more per 1000 (from 1 more to 121 more)	VERY LOW	IMPORTANT
Decrease in eGFR of at least 29-30 mL/min - lifetime cumulative intake: 500-2999g (Curhan 2004)												
1	observational study	no serious risk of bias[5]	no serious inconsistency	serious	no serious imprecision	none	-	6.84%	OR 2.23 (1.36 to 3.66)	72 more per 1000 (from 22 more to 143 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Decrease in eGFR of at least 29-30 mL/min - lifetime cumulative intake: >3000g (Curhan 2004)												
1	observational study	serious[5]	no serious inconsistency		no serious imprecision	none	-	6.84%	OR 2.04 (1.28 to 3.25)	62 more per 1000 (from 18 more to 124 more)	VERY LOW	IMPORTANT
30% or greater decrease in eGFR - lifetime cumulative intake 100-499g (Curhan 2004)												
1	observational study	serious[5]	no serious inconsistency	none	serious[3]	none	-	8.06%	OR 1.4 (0.79 to 2.48)	29 more per 1000 (from 16 fewer to 98 more)	VERY LOW	IMPORTANT
30% or greater decrease in eGFR - lifetime cumulative intake 500-2999g (Curhan 2004)												
1	observational study	serious[5]	no serious inconsistency	none	serious[3]	none	-	8.06%	OR 1.64 (1 to 2.69)	45 more per 1000 (from 0 more to 110 more)-	VERY LOW	IMPORTANT
30% or greater decrease in eGFR - lifetime cumulative intake >3000g (Curhan 2004)												
1	observational study	serious[5]	no serious inconsistency	none	no serious imprecision	none	-	8.06%	OR 2.19 (1.4 to 3.43)	80 more per 1000 (from 29 more to 151 more)	VERY LOW	IMPORTANT
Increased creatinine concentration - 15-1499 pills / 14 years (Kurth 2003)												
1	observational study	serious[1]	no serious inconsistency	none	serious[3]	none	-	-	OR 0.68 (0.48 to 0.96)	-	VERY LOW	IMPORTANT
Increased creatinine concentration - 1500-2499 pills / 14 years (Kurth 2003)												
1	observational study	serious[1]	no serious inconsistency	none	very serious[4]	none	-	-	OR 0.69 (0.31 to 1.54)	-	VERY LOW	IMPORTANT
Increased creatinine concentration - >2500 pills / 14 years (Kurth 2003)												
1	observational	serious[1]	no serious	none	very serious[4]	none	-	-	OR 1.11	-		IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
	study		inconsistency						(0.52 to 2.37)		VERY LOW	
Time to renal replacement therapy (Evans 2009)												
1	observational study	serious[6]	no serious inconsistency	Serious[6]	serious[3]	none	-	-	HR 1.10 (0.90 to 1.34)	-	VERY LOW	IMPORTANT
Risk of renal failure – Overall (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.2 (1.14 to 1.26)	-	VERY LOW	IMPORTANT
Risk of renal failure - First prescription (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.31 (1.03 to 1.67)	-	VERY LOW	IMPORTANT
Risk of renal failure - Long gap (at least 12/12 between prescriptions) (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.21 (1.02 to 1.44)	-	VERY LOW	IMPORTANT
Risk of renal failure - repeat use with low MPR (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.16 (1.04 to 1.29)	-	VERY LOW	IMPORTANT
Risk of renal failure - repeat use with medium MPR (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.27 (1.1 to 1.47)	-	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Control	Relative (95% CI)	Absolute		
Risk of renal failure - repeat use with high MPR (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	-	RR 1.44 (1.18 to 1.76)	-	VERY LOW	IMPORTANT
Risk of renal failure - repeat use with very high MPR (De Vries 2010)												
1	observational study	Serious[2]	no serious inconsistency	none	serious[3]	none	-	0%	RR 1.34 (1.15 to 1.56)	-	VERY LOW	IMPORTANT

1 Kurth (2003) assessed number of pills taken, not dose of paracetamol and did not report Hazard Ratios
2 Unclear whether DeVries (2010) accounted for all essential confounders identified by the GDG and the study did not report Hazard Ratios
3 Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in one direction making the effect size uncertain
4 Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes. The confidence intervals crossed the MID in both directions making the effect size very uncertain
5 The study did not report Hazard Ratios
6 Participants in Evans (2009) had raised creatinine at study entry.

Table S7: Excluded Studies

Reference	Reason for exclusion
AHLERS2011[7]	Short term study in healthy volunteers
ALDOORI 1998 [9]	Incidence of diverticular disease. 4 years of follow up.
AMBERBIR2011[18]	Paracetamol and risk of allergic diseases (asthma, eczema, sensitisation).

Reference	Reason for exclusion
ANON 2012[1]	Article/ review summary
BARR 2004[35]	Use of paracetamol associated with new diagnosis of asthma 1990-1996.
BARRETT 1996[36]	Review of chronic renal outcomes associated with paracetamol
BLOT 2000[66]	Case control study of GI bleeding
CARRICK 1984[99]	Randomised trial of solprin vs. paracetamol. Followed up 24 hours post operatively.
CARVAJAL 1996[100]	Comparison of toxicity profiles of paracetamol and aspirin
CASTELEO2000[102]	Risk of bladder cancer with paracetamol use.
CHANG 2004[105]	Risk of Hodgkins lymphoma with paracetamol use
CURHAN 2002[138]	Study does not report adverse events of paracetamol.
DAVEY 2005[145]	Risk of allergic symptoms with paracetamol use.
DERBY 1996[160]	Incidence of renal and bladder cancer with use of paracetamol..

Reference	Reason for exclusion
DUBACH 1983[174]	Abuse of phenacetin containing analgesics- not specifically paracetamol
ELFSTROM 1999[179]	RCT of single dose of paracetamol and the incidence of GI Aes. Population was healthy volunteers. 4 hour follow up
ENELI 2005[180]	Review of studies assessing risk of cancer with paracetamol use.
FAULKNER 1988[190]	Study about aspirin only.
FORED 2001[193]	Case control study of risk of chronic renal failure
FRIIS 2002[201]	Incidence of cancers with paracetamol use.
GAGO 1999[205]	Risk of renal cell carcinoma with paracetamol use.
GALLERANI 2004[206]	Case control study of incidence of UGIB
GARCIA 2001A[209]	Review of previously published data.
GAULT 1998[212]	Review of analgesic nephropathy
GENKINGER 2007[215]	incidence of bladder cancer with use of paracetamol

Reference	Reason for exclusion
GONZALEZPEREZ2006[224]	Review
GRAHAM 2005[230]	Review of paracetamol (kinetics and toxicity)
HAWKER 2010[241]	Abstract
KAYE 2001[292]	Incidence of renal and bladder cancer with use of paracetamol
KELKAR 2012[294]	Case control study of incidence of renal disease
KREIGER 1993[305]	Incidence of renal cell carcinoma risk with paracetamol use
LANAS 2003[318]	Case control study of risk of GI bleeding associated with paracetamol.
LAPORTE 1991[320]	Case control study of risk of GI bleeding associated with paracetamol.
LEVY 1988[330]	Case control study of risk of GI bleeding associated with paracetamol.
LEWIS 2002[331]	Meta-analysis of individual patient data from 3 retrospective Case control study of risk of GI bleeding associated with paracetamol.
LINET 1995[334]	Risk of renal pelvis and ureter cancer risk with use of analgesics

Reference	Reason for exclusion
LIVOTI 1997[332]	Reasons for endoscopy for GI bleeds
MCCREDIE 1988[369]	Risk of urothelial, renal pelvis or bladder cancer incidence and paracetamol use.
MCCREDIE 1995[368]	Risk of renal cell cancer and paracetamol use
MCKEEVER 2005[375]	Risk of asthma, COPD, and FEV with use of paracetamol
MCLAUGHLIN 1998[377]	Review of case control studies assessing analgesic use and CRF
MITCHELL 2011[393]	N too low (N=50)
MOORE 2013[398]	Case population substudy in France. No overall n quoted for population from which cases derived
MORIDE 2005[403]	Study focus is to determine whether risk factors for upper G bleeding influenced prescription of COX2 inhibitors and NSAIDS.
NEAFSEY 2004[421]	Summary of treatment
O'RIORDAN 2011[429]	Study to determine prevalence of Aki in people with paracetamol- induced hepatotoxicity
PERNEGER 1994[446]	Case control study of paracetamol use and incidence of ESRD.

Reference	Reason for exclusion
POMMER1989[458]	Case control study of paracetamol use and incidence of ESRD.
RAHME 2000[466]	Economic study (see Rahme 2002)
REXRODE 2001[482]	Duplication of Kurth (2003)
ROLANDO 1990[486]	AKI associated with bacterial infection
ROSENBERG 1998[490]	Risk of transitional cell or renal cell cancer with paracetamol use
SABATE 2011[496]	Case series
SANDER 1989[501]	Case control study of risk of chronic renal disease
SERRIE 2009[517]	Abstract only, paracetamol-tramadol combination
SHAHEEN2000[518]	Risk of asthma associated with paracetamol use
SHRIVASTAVA 2013[525]	207 males and 129 females reporting adverse drug reactions; n<1000 agreed cut off for observational data
STURKENBOOM 2005[547]	Wrong population- Children (0-14 years)

Reference	Reason for exclusion
VENTURA 1999[575]	Study focus on Adverse Drug Reaction- participants underwent drug challenge
WAKSMAN 2007[578]	Review of NSAIDS and cardiovascular risk
WALTER 2011[579]	Association between paracetamol and incident malignancies
WALTER 2011A[580]	Association between paracetamol use and haematological malignancy.
YATES 1984[603]	Reports number and type of side effects reported for each drug. No outcomes of interest.