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Prescribing of paracetamol in patients with chronic renal failure

A Drug Utilisation Study

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1. Background

Sweden's national competent authority is performing a review to analyse data in support of the recommendation to reduce the maximal dose for paracetamol in case of renal insufficiency, which is recommended in most but not all of the Summary of Product Characteristics (SmPCs) for paracetamol containing medicinal products in Sweden. In patients with a glomerular filtration rate (GFR) of 10-50 ml/min it is recommended to reduce the maximum dose to 2 grams per day and in patients with a GFR <10 ml/min to 1.5 grams per day. There is a similar situation in the United Kingdom where some SmPCs give the same specific dosage recommendations based on GFR, whilst others simply advise care when administering to patients with renal impairment. Also in Germany dosage recommendations for paracetamol based on GFR were provided for some but not all paracetamol-containing medicinal products.

It is, however, unknown to what extent the dose of paracetamol is lowered in clinical practice in patients with reduced renal function, and whether there is an increased risk of paracetamol toxicity/hepatic injury associated with use of paracetamol in patients with reduced renal function.

This study used two in-house electronic health record databases available at the European Medicines Agency (EMA), the IQVIA Medical Research Data-UK (IMRD-UK, formerly the THIN database), and the IQVIA Medical Research Data-France and Germany (IMRD-Germany, formerly IMS-Germany) in order to describe, analyse and compare paracetamol doses in adult patients with and without chronic renal failure (CRF).

2. Objectives

The study had the following aims:

- To review and compare daily, maximum daily and total doses of paracetamol among paracetamol prescriptions in the following groups:
 - a) Patients with a diagnosis of CRF vs. the same patients one year or more before the diagnosis
 - b) Patients with a diagnosis of CRF vs. patients without a diagnosis of CRF at anytime
 - c) Patients with CRF stratified by severity of renal failure (stages 1-2, 3, 4 and 5)

3. Methods

3.1. Databases and settings

Version September 2018 of the IMRD database and version December 2018 of IMRD Germany was used for the study. A third in-house database available at EMA, IMRD- France, was not included in the study due to a low number of patients with a recorded diagnosis of chronic renal failure (<12,000 patients).

In IMRD Germany the study was restricted to general practitioner (GP) practices. The study period was 1 January 2000 to 31 December 2018 in IMRD FRANCE and 1 January 2000 to 25 September 2018 in IMRD UK. A minimum of 1 year "lookback" prior to date of prescribing for each prescription was required to allow adequate time for recording of CRF. In IMRD Germany, patients included in the study were 45 years or older.

In IMRD UK the analyses were restricted to those aged 60 years and older. This is because a prescription charge applies below this age, which modifies the patterns of use towards the over-the-

counter paracetamol, thus making patients below 60 years unrepresentative of paracetamol users. A sensitivity analysis in patients below 60 years will be performed.

3.2. Identification of paracetamol products

In IMRD Germany all solid oral and rectal administration forms with a recorded strength were included, selecting those products for which paracetamol was the only active substance. The EphMRA ATC code system is used in IMRD. All medicinal products with a known composition have an EphMRA ATC code and substance name/s for the ingredients in the product. All liquid formulations were excluded.

In IMRD UK paracetamol products will be selected from all paracetamol monotherapy preparations (combination preparations were excluded as the daily dose might be restricted by the other constituent). Only 500 mg oral dosage forms were included in IMRD UK as there is a risk of confounding with other dosage forms and dose information is better recorded for tablets (which account for 81.1% of paracetamol prescriptions in IMRD UK 1809).

Lists of included paracetamol products are provided in Appendix 4.

3.3. Daily, maximum daily and total doses prescribed

Information about the calculation of daily, maximum daily and total doses in IMRD UK and IMRD Germany is provided in appendix 2.

The mean daily dose in mg and the mean total dose in mg per prescription were calculated among all prescriptions for paracetamol. The proportion of prescriptions was categorised into the following daily dose categories for daily and maximum daily dose: 0 – 2 g daily, 2.1 – 3.9 g daily, and 4g daily.

3.4. Comparisons

Mean daily doses and mean total doses in mg among paracetamol prescriptions was calculated and compared in the following groups:

- Patients with CRF vs. patients without CRF
- Patients with CRF by CRF stage (stage 1-2, 3, 4, and 5)
- Patients with CRF vs. the same patients one or more years prior to the CRF (only in IMRD UK)

In IMRD UK, the comparison between patients with CRF and patients without CRF include patients matched on year of birth, year prescribed and sex. In IMRD Germany, the main analysis included all patients, with a matched analysis performed as a sensitivity analysis.

In IMRD Germany daily doses were only available in around 20% of paracetamol prescriptions, varying from practice to practice, whereas total doses are available and can be compared among all paracetamol prescriptions. A separate comparison of daily doses in patients with CRF vs. patients without CRF restricted to practices with a minimum frequency of reported paracetamol doses of 10% was performed as a sensitivity analysis.

To see if paracetamol dose in renal failure is affected by liver failure, a sensitivity analysis was performed excluding patients with prior liver failure.

In IMRD Germany the representativeness of paracetamol prescriptions with a reported daily dose was assessed by comparing the total dose of paracetamol in prescriptions with a daily dose compared to prescriptions without a reported daily dose.

4. Results

4.1. Paracetamol prescribing in all patients

4.1.1. IMRD Germany

In GP practices in IMRD Germany during the study period between 1 January 2000 and 31 December 2018, there were a total of 1,206,741 prescriptions for plain paracetamol products. Of those, 294,861 prescriptions concerned non-liquid formulations of paracetamol that contained information about the paracetamol strength in a total of 177,737 patients aged 45 years or older with at least 365 days of observation prior to the prescription.

The mean number of prescriptions per patient was 1.66 (median 1) and the maximum number of prescriptions per patient was 171. The mean age at the time of prescription was 65.1 years. Women accounted for 57.5% of the prescriptions and 55.5% of the patients. A total of 58 prescriptions had a calculated daily dose exceeding 4 grams per day and were excluded, leaving a total of 294,803 paracetamol prescriptions in 177,715 patients available for analysis of which a daily dose could be calculated in 59,126 prescriptions (20.1%). The mean total dose was slightly higher among prescriptions where dose could be calculated compared to prescriptions where dose could not be calculated, mean dose 11,961.9 mg (standard deviation 7276.1 mg) vs. mean dose 11,785.2 mg (standard deviation 5887.8 mg).

Mean daily doses were significantly higher in males compared to females. Mean daily doses were highest in the age group 70-79 years. Mean total doses were higher in females compared to males, and were highest in older age groups.

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older in IMRD Germany are shown in table 1.

4.1.2. IMRD UK

In GP practices in IMRD UK during the study period for 1 January 2000 to 25 September 2018, there were a total of 29,638,849 prescriptions for monotherapy paracetamol products. Of those, 19,537,064 prescriptions were for 500mg solid oral dosage formulations of paracetamol in a total of 1,204,794 patients aged 45 years or older with at least 365 days of observation prior to the prescription. The mean number of prescriptions per patient was 13.0 (median 2) and the maximum number of prescriptions per patient was 1415.

The mean age at the time of prescription was 73.3 years. Women accounted for 64.8% of the prescriptions. A daily dose could be calculated in 5,791,761 prescriptions. A total of 235 prescriptions had a calculated daily dose exceeding 4 grams per day and were excluded, leaving a total of 5,791,526 paracetamol prescriptions in 431,073 patients available for analysis of which a daily dose could be calculated for (29.6% of all prescriptions). A maximum daily dose could be calculated for 12,236,149 prescriptions from 849,569 patients (62.6% of all prescriptions).

The mean total dose was slightly higher among prescriptions where dose could be calculated compared to prescriptions where dose could not be calculated, mean dose 61.2 g (standard deviation 31.8 g) vs. mean dose 60.9 g (standard deviation 29.0 g).

Mean calculated daily and total doses varied by age group, gender and year of the prescription: see Appendix 6. Mean daily doses were similar in males and females and mean daily doses were highest in

the younger age group. There was a trend towards increasing mean daily doses over time between the years 2000 to 2018.

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older in IMRD UK are shown in table 2. The calculated maximum daily doses in paracetamol prescriptions in patients 45 years or older in IMRD UK are shown in Table 3.

4.2. Paracetamol prescribing in patients with CRF

4.2.1. IMRD Germany

In IMRD Germany, a total of 23,952 paracetamol prescriptions in 13,257 patients were issued on or after the first recorded chronic renal failure (CRF) diagnosis (8.1% of included paracetamol prescriptions and 7.5% of patients with a paracetamol prescription). The mean age at the time of prescription was 77.5 years. Women accounted for 61.8% of the prescriptions and 58.2% of the patients.

Daily dose could be calculated in 19.9% of paracetamol prescriptions issued on or after a diagnosis of CRF (4761 out of 23,952 prescriptions).

The mean total dose was higher among prescriptions where dose could be calculated compared to prescriptions where dose could not be calculated, 14,518.1 mg (standard deviation 10,584.2 mg) vs. 12,345.3 mg (standard deviation 6986.2 mg).

There was no significant difference in mean daily doses between males and females. Mean daily doses were highest in younger age groups. There was no evidence of decreasing mean daily doses over time between the years 2000 to 2018.

Mean total doses were also similar in males and in females, and were highest in older age groups. The highest mean total doses were observed between 2005 and 2008.

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older with CRF are shown in table 1.

4.2.2. IMRD UK

In IMRD UK a total of 3,756,338 paracetamol prescriptions in 213,304 patients over the age of 45 were issued on or after the first recorded chronic renal failure (CRF) diagnosis (21.4% of all paracetamol prescriptions and 18.4% of patients with a paracetamol prescription). The mean age at the time of prescription was 79.6 years. Women accounted for 69.0% of the prescriptions.

Daily dose could be calculated in 26.9% of paracetamol prescriptions issued on or after a diagnosis of CRF (1,011,954 out of 3,756,338 prescriptions). Maximum daily dose could be calculated in 57.5% of paracetamol prescriptions issued on or after a diagnosis of CRF (2,159,671 of 3,756,338 prescriptions).

The mean total dose was similar among prescriptions where dose could be calculated compared to prescriptions where dose could not be calculated, 61.5g (standard deviation 33.8g) vs. 61.5g (standard deviation 30.3g).

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older in patients with CRF in IMRD UK are shown in table 2. The calculated maximum daily doses in paracetamol prescriptions in patients 45 years or older, with CRF and without CRF in IMRD UK are shown in Table 3.

For mean calculated daily and total doses by age group, gender and year of the prescription, see Appendix 7.

4.3. Paracetamol prescribing in patients without CRF

4.3.1. IMRD Germany

In IMRD Germany, a total of 252,577 prescriptions concerned 155,135 patients who never had a diagnosis of CRF. The mean age at the time of prescription was 63.5 years. Women accounted for 57.7% of the prescriptions and 55.8% of the patients.

Daily dose could be calculated in 20.0% of paracetamol prescriptions in patients who never had a diagnosis of CRF (50,609 out of 252,577 prescriptions). The mean total dose was slightly lower among prescriptions where dose could be calculated compared to prescriptions where dose could not be calculated, 11,557.3 mg (standard deviation 6660.8 mg) vs. 11,699.2 mg (standard deviation 5816.6 mg).

Mean daily doses were significantly higher in males compared to females. Mean daily doses were highest in younger age groups. There was a trend towards decreasing mean daily doses over time between the years 2000 to 2018.

Mean total doses were higher in females compared to males, and were highest in older age groups. Mean total doses were higher between 2000 and 2008 compared to 2009 to 2018.

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older, without CRF in IMRD Germany, are shown in Table 1.

In IRMD UK, a total of 13,804,286 prescriptions concerned 946,270 patients who never had a diagnosis of CRF. The mean age at the time of prescription was 71.6 years. Women accounted for 64.2% of the prescriptions.

The calculated mean and median daily dose and the percentage of prescriptions with a calculated daily dose of up to 2 grams, more than 2 grams to less than 4 grams, and 4 grams are shown in Table 3.

A crude comparison of the mean daily dose and maximum daily dose show that both are slightly higher in renal failure than without renal failure

The calculated mean and median daily doses and the percentage of prescriptions with a calculated daily dose in the defined categories for patients 45 years or older in patients without CRF in IMRD UK are shown in table 2. The calculated maximum daily doses in paracetamol prescriptions in patients 45 years or older, with CRF and without CRF in IMRD UK are shown in Table 3.

For mean calculated daily and total doses by age group, gender and year of the prescription, see Appendix 8.

Table 1. Calculated daily doses in paracetamol prescriptions in patients 45 years or older, with CRF and without CRF in IMRD Germany

Prescriptions with a calculated dose up to 4g			
	Patients 45 years or older	Patients 45 years or older with CRF*	Patients 45 years or older without CRF*
Total no. of prescriptions:	59,126 (20.1%)	4761 (19.9%)	50,609 (20.0%)
<i>Patients 45-59 years</i>	28,329 (22.7%)	549 (23.5%)	26,943 (22.6%)
<i>Patients ≥60 years</i>	30,797 (18.1%)	4212 (19.5%)	23,666 (17.7%)
Mean daily dose (SD):	1565.3 mg (623.2 mg)	1674.2 mg (684.4 mg)	1550.8 mg (615.3 mg)
<i>Patients 45-59 years</i>	1564.4 mg (615.6 mg)	1747.0 mg (721.5 mg)	1558.3 mg (612.8 mg)
<i>Patients ≥60 years</i>	1566.2 mg (630.1 mg)	1664.7 mg (678.0 mg)	1542.3 mg (618.1 mg)
Median daily dose (IQR):	1500 mg (1000-1500 mg)	1500 mg (1500-2000 mg)	1500 mg (1000-1500 mg)
<i>Patients 45-59 years</i>	1500 mg (1000-1500 mg)	1500 mg (1500-2000 mg)	1500 mg (1000-15000 mg)
<i>Patients ≥60 years</i>	1500 mg (1000-1500 mg)	1500 mg (1500-2000 mg)	1500 mg (1000-15000 mg)
No. of prescriptions with DD = 4 g:	513 (0.9%)	111 (2.3%)	381 (0.8%)
<i>Patients 45-59 years</i>	199 (0.7%)	21 (3.8%)	171 (0.6%)
<i>Patients ≥60 years</i>	314 (1.0%)	90 (2.1%)	210 (0.9%)
No. of prescriptions with DD >2-<4 g:	6476 (11.0%)	520 (10.9%)	5519 (10.9%)
<i>Patients 45-59 years</i>	3367 (11.9%)	72 (13.1%)	3207 (11.9%)
<i>Patients ≥60 years</i>	3109 (10.1%)	456 (10.8%)	2312 (9.8%)
No. of prescriptions with DD ≤ 2 g:	52,137 (88.2%)	4130 (86.7%)	44,709 (88.3%)
<i>Patients 45-59 years</i>	24,763 (87.4%)	448 (81.6%)	23,565 (87.5%)
<i>Patients ≥60 years</i>	27,374 (88.9%)	3674 (87.2%)	21,144 (89.3%)

DD = daily dose, g = grams, GP = general practitioner, IQR = interquartile range, mg = milligrams, SD = standard deviation

* prescriptions from patients before their diagnosis of renal failure are not counted

Table 2. Calculated daily doses in paracetamol prescriptions in patients 45 years or older, with CRF and without CRF in IMRD UK

Prescriptions with a calculated dose up to 4g			
	Patients 45 years or older	Patients 45 years or older with CRF*	Patients 45 years or older without CRF*
Total no. of prescriptions:	5,791,526 (29.6%)	1,011,952 (26.9%)	4,101,216 (29.7%)
<i>Patients 45-59 years</i>	842,436 (29.1%)	37,779 (28.1%)	757,048 (28.8%)
<i>Patients ≥60 years</i>	4,949,090 (29.7%)	974,173 (26.9%)	3,344,168 (29.9%)

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Prescriptions with a calculated dose up to 4g			
Mean daily dose (SD): <i>Patients 45-59 years</i> <i>Patients ≥60 years</i>	3305 mg (616.6 mg) 3360 mg (548.7 mg) 3296 mg (626.9 mg)	3330 mg (651.2 mg) 3415 mg (541.1 mg) 3327 mg (654.9 mg)	3304 mg (611.5 mg) 3359 mg (548 mg) 3292 mg (624.3 mg)
Median daily dose (IQR): <i>Patients 45-59 years</i> <i>Patients ≥60 years</i>	3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg)	3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg)	3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg) 3000 mg (3000-4000 mg)
No. of prescriptions with DD = 4 g: <i>Patients 45-59 years</i> <i>Patients ≥60 years</i>	2,159,109 (37.3%) 327,856 (38.9%) 1,831,253 (37%)	415,158 (41%) 16,391 (43.4%) 398,767 (40.9%)	1,515,854 (37%) 293,629 (38.8%) 1,222,225 (36.5%)
No. of prescriptions with DD >2-<4 g: <i>Patients 45-59 years</i> <i>Patients ≥60 years</i>	3,337,697 (57.6%) 495,512 (58.8%) 2,842,185 (57.4%)	534,863 (52.9%) 20,821 (55.1%) 514,042 (52.8%)	2,382,298 (58.1%) 446,206 (58.9%) 1,936,092 (57.9%)
No. of prescriptions with DD ≤ 2 g: <i>Patients 45-59 years</i> <i>Patients ≥60 years</i>	294,720 (5.1%) 19,068 (2.3%) 275,652 (5.6%)	61,931 (6.1%) 567 (1.5%) 61,364 (6.3%)	203,064 (5%) 17,213 (2.3%) 185,851 (5.6%)

DD = daily dose, g = grams, GP = general practitioner, IQR = interquartile range, mg = milligrams, SD = standard deviation; * prescriptions from patients before their diagnosis of renal failure are not counted

Table 3. Calculated maximum daily doses in paracetamol prescriptions in patients 45 years or older, with CRF and without CRF in IMRD UK

Prescriptions with a calculated maximum daily dose up to 4g			
	Patients 45 years or older	Patients 45 years or older with CRF*	Patients 45 years or older without CRF*
Total no. of prescriptions:	12,236,149 (62.6%)	2,159,671 (57.5%)	8,680,242 (62.9%)
<i>Patients 45-59 years</i>	1,767,891 (61.1%)	80,598 (59.9%)	1,595,629 (60.8%)
<i>Patients ≥60 years</i>	10,468,258 (62.9%)	2,079,073 (57.4%)	7,084,613 (63.4%)
Mean daily dose (SD):	3798 mg (673.1 mg)	3821 mg (626 mg)	3802 mg (667.3 mg)
<i>Patients 45-59 years</i>	3849 mg (595.1 mg)	3882 mg (538.8 mg)	3853 mg (585.3 mg)
<i>Patients ≥60 years</i>	3790 mg (685 mg)	3818 mg (629 mg)	3790 mg (683.9 mg)
Median daily dose (IQR):	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)
<i>Patients 45-59 years</i>	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)
<i>Patients ≥60 years</i>	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)	4000 mg (4000-4000 mg)
No. of prescriptions with DD = 4 g:	11,046,651 (90.3%)	1,965,711 (91%)	7,849,309 (90.4%)
<i>Patients 45-59 years</i>	1,639,995 (92.8%)	76,330 (94.7%)	1,481,989 (92.9%)
<i>Patients ≥60 years</i>	9,406,656 (89.9%)	1,889,381 (90.9%)	6,367,320 (89.9%)
No. of prescriptions with DD >2-<4 g:	416,445 (3.4%)	70,672 (3.3%)	292,665 (3.4%)
<i>Patients 45-59 years</i>	47,241 (2.7%)	1,279 (1.6%)	43,132 (2.7%)
<i>Patients ≥60 years</i>	369,204 (3.5%)	69,393 (3.3%)	249,533 (3.5%)
No. of prescriptions with DD ≤ 2 g:	773,053 (6.3%)	123,288 (5.7%)	538,268 (6.2%)
<i>Patients 45-59 years</i>	80,655 (4.6%)	2,989 (3.7%)	70,508 (4.4%)
<i>Patients ≥60 years</i>	692,398 (6.6%)	120,299 (5.8%)	467,760 (6.6%)

DD = daily dose, g = grams, GP = general practitioner, IQR = interquartile range, mg = milligrams, SD = standard deviation; * prescriptions from patients before their diagnosis of renal failure are not counted

4.4. Paracetamol prescribing by degree of CRF

The procedure for assigning the CRF stage over time is described in Appendix 3.

In IMRD Germany, mean daily and total paracetamol doses by CRF stage are shown in Table 4. There were significant differences in mean daily doses and mean total doses by CRF stage. Mean daily doses were highest among patients with less severe renal failure, i.e. chronic renal failure stages 1-2. Mean total doses were highest in patients with chronic renal failure stages 3-5.

In IMRD UK, mean daily and total paracetamol doses by CRF stage are shown in Table 5. Mean daily doses, mean maximum daily dose and mean total dose were all highest among patients with less severe renal failure. In all cases there is a trend towards lower doses with more severe renal failure as measured by eGFR.

Table 4 Mean daily and total doses of paracetamol in patients with renal failure by CRF stage in IMRD Germany

	Mean daily dose (No.)	Mean total dose (No.)
CRF stage 5	1666.0 mg (N=61)	13,306.8 mg (N=489)
CRF stage 4	1535.3 mg (N=177)	13,175.1 mg (N=948)
CRF stage 3	1747.2 mg (N=877)	13,324.4 mg (N=4062)
CRF stage 1-2	1845.2 mg (N=771)	11,606.7 mg (N=3760)
Unknown CRF stage	1614.8 mg (N=2875)	12,882.2 mg (N=14,693)

CRF = chronic renal failure

Table 5 Mean daily and total doses of paracetamol in patients with renal failure by CRF stage in IMRD UK *

CRF Stage**	Mean daily dose (No.)	Maximum daily dose (No.)	Mean total dose (No.)
CRF stage 5	3294 mg (N=8,066)	3816 mg (N=18,420)	58.0 g (N=31,305)
CRF stage 4	3334 mg (N=61,909)	3806 mg (N=133,481)	58.4 g (N=232,440)
CRF stage 3	3327 mg (N=541,914)	3825 mg (N=1,175,422)	60.7 g (N=2,042,041)
CRF stage 1-2	3360 mg (N=153,051)	3854 mg (N=334,148)	62.2 g (N=598,059)
Unknown CRF stage	not calculated	not calculated	not calculated

CRF = chronic renal failure; eGFR = estimated glomerular filtration rate

* This analysis uses the most recent eGFR in the year prior to prescribing. If there is no eGFR recorded in this time, the prescription is excluded from the analysis. ** Stage 5 most serious disease, Stage 1-2 least serious disease.

4.5. Comparing patients with and without CRF

4.5.1. IMRD Germany

In IMRD Germany, mean daily and total doses of paracetamol were significantly higher among prescriptions from patients with renal failure vs. patients without renal failure. In line with this finding, there was also a higher proportion of daily doses of 4 grams per day among prescriptions from patients



with renal failure vs prescriptions from patients without renal failure. Results were similar in practices where the dose of paracetamol was recorded in at least 10% of paracetamol prescriptions except for a slightly lower mean total dose of paracetamol in patients with renal failure in those practices. These results are shown in Appendix 4.

Results from an analysis comparing prescriptions in patients with CRF to prescriptions in patients without CRF, matched 1:1 on age, gender and year of prescription are shown in Table 2 in Appendix 4. Results are similar to results from all patients.

Results from an analysis in patients with CRF to prescriptions in patients without CRF, excluding patients with prior liver failure, are shown in Appendix 4. Again, results are similar to results from all patients.

4.5.2. IMRD UK

In IMRD UK, mean daily and total doses of paracetamol were marginally higher among prescriptions from patients with renal failure vs. patients without renal failure. The maximum daily doses were similar. In line with this finding, there was also a higher proportion of daily doses of 4 grams per day among prescriptions from patients with renal failure vs prescriptions from patients without renal failure. Results were similar when excluding patients with serious-moderate liver disease

Results from the analysis comparing prescriptions in patients with CRF to prescriptions in patients without CRF, matched 1:1 on age, gender and year of prescription are shown in Table 6.

Table 6. Between prescription comparisons of mean daily dose, maximum daily dose & total dose in matched prescriptions with and without history of renal failure in IMRD UK. *

Cohort	n matched	n not matched	% not matched	mean paracetamol dose ^(g)	
				with renal failure	without renal failure
daily dose					
all patients	965,420	6,923	0.7%	3.33	3.31
excluding moderate-serious liver disease	959,455	6,947	0.7%	3.33	3.31
maximum daily dose					
all patients	2,071,809	3,265	0.2%	3.82	3.82
excluding serious-moderate liver disease	2,058,172	3,243	0.2%	3.82	3.82
total dose					
all patients	3,609,210	5,077	0.1%	61.5	61.4
excluding serious-moderate liver disease	3,582,975	5,102	0.1%	61.5	61.4

* Prescriptions matched 1:1 on age, sex & year of prescribing

4.6. Within patients comparison– IMRD UK only

An analysis within patients before and after diagnosis of renal failure showed the mean daily doses, mean maximum daily doses and mean total daily doses were higher after the diagnosis of renal failure (table 7). The exclusion of patients with serious or moderate liver disease had little impact on the results.

Table 7. Within patient comparisons of mean daily dose, maximum daily dose & total dose before and after diagnosed chronic kidney disease. #

total dose before and after diagnosed chronic kidney disease.				
mean paracetamol dose				
(g)				
	patients	prescriptions	before without renal failure	after with renal failure
daily dose				
all patients	20,103	741,287	3.26	3.30
excluding serious / moderate liver disease	19,950	736,366	3.26	3.30
maximum daily dose				
all patients	49,838	1,765,803	3.74	3.81
excluding serious / moderate liver disease	49,470	1,754,490	3.74	3.81
total dose				
all patients	78,783	2,973,282	58.4	60.8
excluding serious / moderate liver disease	78,167	2,951,009	58.4	60.9

Patients are only included in this analysis if they had paracetamol prescribed before and after the first record of chronic kidney disease. Prescriptions from the year immediately prior to first coding for renal failure are excluded.

5. Conclusion

This study shows that mean daily prescribed paracetamol doses and mean maximum daily doses were higher in patients with chronic renal failure compared to patients without chronic renal failure.

When comparing prescriptions on patients matched by age, sex and year of prescribing, there was only a slightly higher mean daily dose of paracetamol in chronic renal failure, no difference in maximum daily dose and very little difference in mean total dose. Comparing paracetamol doses within patients before and after the diagnosis of chronic renal failure also showed a slightly higher mean daily dose, maximum daily dose and total dose after the diagnosis of chronic renal failure.

However, within the group of patients diagnosed with chronic renal failure paracetamol daily and maximum daily doses were lower in patients with severe renal failure (i.e. with lower eGFR) compared to patients with milder forms of renal failure, with a trend of lower doses with increasing severity of renal failure, which might reflect an attempt to adjust doses in patients with severe renal failure, although this finding is based on limited data in patients with severe renal failure.

These findings should be viewed against a background trend of increasing paracetamol dose with time, perhaps reflecting changing practice to more “rational” prescribing of analgesia and a move away from NSAIDs. This might account for the higher mean dose in the within and crude between patient comparisons. NSAIDs are less likely to be used following diagnosis of renal failure and this could impact on whether and at what dose paracetamol is used.

There is little evidence to support the suggestion that prescribers use different dose of paracetamol in patients with chronic renal failure and opposed to patients without renal failure. However, in patients with chronic renal failure there is evidence that more severe kidney disease is associated with lower doses of paracetamol. These findings were not found to be confounded by comorbid liver disease (data not shown).

An important weakness in this study is that daily paracetamol doses were only recorded in around 20% of paracetamol prescriptions in IMRD Germany, and 30% in IMRD UK, and there was some evidence that paracetamol prescriptions with a recorded dose were not representative of all paracetamol prescriptions in terms of total paracetamol doses. The dose could be calculated in a similar proportion of prescriptions in patients with and without renal failure, whereas the proportion of prescriptions where dose could be calculated was lower in patients with severe renal failure.

Total paracetamol doses, i.e. the total amount of paracetamol prescribed, could be calculated in all prescriptions, but they are influenced not only by the daily dose but also by the duration of treatment, and are therefore considered to have limited value for the analysis.

Lastly, something important to note is the results in this study are descriptive and do not imply causality. It is possible that patients with renal failure have a higher frequency of comorbidities that require higher doses of paracetamol or that paracetamol doses are higher due to fewer available alternative analgesics for treatment of pain in patients with renal failure. However, no attempt was made to investigate any association between renal failure and comorbid painful conditions.

Appendix (1) Definition of chronic renal failure

Identification of patients with chronic renal failure in IMRD Germany

Patients with CRF will be selected from the ICD 10 codes N18.1 (Chronic kidney disease, stage 1, normal or increased), N18.2 (Chronic kidney disease, stage 2, GFR 60-89 ml/min), N18.3 (Chronic kidney disease, stage 3, GFR 30-59 ml/min), N18.4 (Chronic kidney disease, stage 4, GFR 15-29 ml/min), N18.5 (Chronic kidney disease, stage 5, end stage kidney disease), N18.9 (Chronic kidney disease, unspecified), N19.0 (Unspecified kidney failure), and I12.0 (kidney failure due to hypertension). Results will be restricted to patients with a diagnostic certainty of 'confirmed' or 'condition after' in order to select only patients with a confirmed diagnosis. In patients with an ICD code of N18.9, N19.0 and I12.0 the degree of renal failure will be estimated, if possible, from the recorded eGFR value.

Identification of patients with CRF in IMRD UK1809

Renal failure will be assessed according to presence of chronic kidney disease codes as identified and validated by Denburg *et al* (<https://doi.org/10.1002/pds.2203> - see table below). Prescriptions dated after a first ever Read code for chronic renal failure will be considered prescribed in renal failure. Otherwise prescriptions are considered not prescribed in renal failure. Individual patients can thus contribute both renal-failure and renal-failure-free prescriptions.

Table 1. Chronic kidney disease Read codes in IMRD UK as validated by Denburg *et al*

medcode	Frequency	Percent
14V2.00 H/O: renal dialysis	1939	0.16
1Z1..00 Chronic renal impairment	19748	1.63
1Z12.00 Chronic kidney disease stage 3	489898	40.53
1Z13.00 Chronic kidney disease stage 4	54286	4.49
1Z14.00 Chronic kidney disease stage 5	11147	0.92
1Z15.00 Chronic kidney disease stage 3A	24922	2.06
1Z16.00 Chronic kidney disease stage 3B	11194	0.93
1Z1B.00 Chronic kidney disease stage 3 with proteinuria	3752	0.31
1Z1C.00 Chronic kidney disease stage 3 without proteinuria	14657	1.21
1Z1E.00 Chronic kidney disease stage 3A without proteinuria	12427	1.03
1Z1G.00 Chronic kidney disease stage 3B without proteinuria	4655	0.39
1Z1H.00 Chronic kidney disease stage 4 with proteinuria	1420	0.12
1Z1J.00 Chronic kidney disease stage 4 without proteinuria	1650	0.14
4519.00 Deteriorating renal function	525	0.04
66i..00 Chronic kidney disease monitoring	89497	7.40
6AA..00 Chronic kidney disease annual review	77572	6.42
7A60100 Creation of arteriovenous fistula NEC	1754	0.15
7L1A.11 Dialysis for renal failure	3235	0.27
7L1A000 Renal dialysis	1667	0.14
7L1A100 Peritoneal dialysis	2949	0.24
7L1A200 Haemodialysis NEC	5458	0.45
7L1B000 Insertion of ambulatory peritoneal dialysis catheter	770	0.06
7L1B100 Removal of ambulatory peritoneal dialysis catheter	330	0.03
8L50.00 Renal transplant planned	595	0.05
90t..00 Chronic kidney disease monitoring administration	8377	0.69

medcode	Frequency	Percent
9Ot0.00 Chronic kidney disease monitoring first letter	157755	13.05
9hE..00 Exception reporting: chronic kidney disease quality indicator	1103	0.09
9hE0.00 Except chronic kidney disease qual indic: Patient unsuitable	47575	3.94
9hE1.00 Exc chronic kidney disease quality indicators: Inform dissent	18365	1.52
D215.00 Anaemia secondary to renal failure	1218	0.10
D215000 Anaemia secondary to chronic renal failure	635	0.05
G22..11 Nephrosclerosis	491	0.04
K05..00 Chronic renal failure	62944	5.21
K05..11 Chronic uraemia	191	0.02
K050.00 End stage renal failure	3970	0.33
K06..00 Renal failure unspecified	33255	2.75
K06..11 Uraemia NOS	1883	0.16
K060.00 Renal impairment	19065	1.58
K060.11 Impaired renal function	8722	0.72
K08..00 Impaired renal function disorder	5200	0.43
K08z.00 Impaired renal function disorder NOS	796	0.07
K0D..00 End-stage renal disease	434	0.04
SP05613 [X] Peritoneal dialysis associated peritonitis	143	0.01
SP08300 Kidney transplant failure and rejection	378	0.03
ZV45100 [V]Renal dialysis status	282	0.02

Appendix (2) Calculation of daily, maximum & total doses

Calculation of daily and total dose in IMRD Germany

From the available information provided by the prescriber, IQVIA calculates a daily dose (i.e. the number of dose forms per day), if possible. The prescribed quantity (i.e. the number of packs prescribed) is provided directly by the physician. Due to difficulty translating information from dosage instructions for liquid formulations because of unclear instructions and use of multiple different measure types such as drops, millilitres, teaspoons etc. that result in a higher risk of incorrectly translated daily doses by IQVIA, this study will be restricted to prescriptions for solid formulations for oral or rectal administration. Paracetamol products with missing strength information will be excluded.

We will calculate the daily dose in mg as the number of dose forms per day multiplied by the strength in mg. Total daily doses above 4000 mg per day will be considered incorrect and will be excluded. No further data cleaning will be performed as it is assumed that the accuracy of the calculated dosage information by IQVIA is not biased with regard to existence or not of a CRF diagnosis.

We will calculate the total dose in mg as the pack size (i.e. number of dose forms per pack) multiplied by the number of packs and the strength in mg.

Calculation of daily, maximum daily and total dose in IMRD UK 1809

Daily doses will be derived from the dosgval field (number of dosage unit taken daily taken from the free text dosage instructions imputed by IMRD UK) to give dose in grams (daily dose = 0.5 x dosgval). Non-specific dosage instructions (e.g. "when required", "as directed") which are present for 70% of all paracetamol prescription will be excluded. Doses over 4g daily (of which there were a small number) will be assumed to be data errors and excluded.

For maximum daily dose the maxdos field will be taken from the enhanced dosages files that are supplied with IMRD UK 1809. This uses the maximum daily dose that is implied in non-specific dosage directions (e.g. "Take 1-2 tablets 4 times a day, when required") and is available for approximately 65% for prescriptions. Where the maxdos field implies a dose of greater than 4g, this will default to 4g and all prescribed paracetamol in the UK is dispensed with a warning not to take for that eight tablets in any 24 hour period.

The calculation of total dose will be calculated as the number of tablets (or capsules) prescribed (always present in IMRD UK) multiplied by 0.5 to give the total dose in grams

Appendix (3) Assignment of stage in patients with CRF

Assignment of CRF stage

The following considerations were made when assigning CRF stage:

In case of more than one CRF stage recorded on the same date, the CRF stage associated with the greatest severity was chosen. The patient was considered to keep the same CRF stage until a new CRF diagnosis was recorded with a different CRF stage. A diagnosis of unknown CRF stage did not change the CRF stage of the patient. The last recorded CRF stage was considered to continue until the end of data.

If the first recorded CRF diagnosis had an unknown CRF stage, then the last eGFR value within 365 days prior to the paracetamol prescription, if available, was used in order to classify the CRF stage.

Patients with chronic renal failure, where the degree of renal failure is not stated in the diagnosis code, will then be classified according to their eGFR, based on the most recent value recorded in the 1-year prior to the date of the prescription:

eGFR (mL/min/1.73m ²)	classification
≥60	normal / mild reduction (stage 1-2)
45-59	mild-moderate reduction (stage 3)
30-44	moderate-severe reduction (stage 3)
15-29	severe reduction (stage 4)
<15	kidney failure (stage 5)

Appendix (4) Codes for identifying paracetamol

Included paracetamol products in IMRD Germany

Therapy No.	Therapy Name	Count
GE10231344	Abalon Tabl 500mg 20 (N2)	6
GE13448141	Apogen Paracet.Alt Tabl 500mg 20 (N2)	10845
GE3492780	Apovit.Apocetamol Tabl 500mg 20 (N2)	12
GE8341363	Ausbuert.Paracetam. Tabl 500mg 20 (N2)	20
GE859196	Ausbuert.Paracetam. Tabl 500mg 30 (N2)	22
GE5012635	Axea Paracetamol Tabl 500mg 30 (N2)	1
GE399903	Ben U Ron (B.A)Alt Kaps 500mg 10 (N1)	126
GE7746	Ben U Ron (B.A)Alt Kaps 500mg 20 (N2)	638
GE1345677	Ben U Ron (B.A)Alt Kaps 500mg 200	6
GE29806	Ben U Ron (B.A)Alt Supp Erw 1000mg 10 (N1)	444
GE426334	Ben U Ron (B.A)Alt Supp Erw 1000mg 100	5
GE955	Ben U Ron (B.A)Alt Supp Kleinkd 250mg 10 (N1)	8
GE157373	Ben U Ron (B.A)Alt Supp Schulkd 500mg 10 (N1)	81
GE1494813	Ben U Ron (B.A)Alt Supp Schulkd 500mg 100	3
GE123805	Ben U Ron (B.A)Alt Supp Sgl 125mg 10 (N1)	7
GE215889	Ben U Ron (B.A)Alt Supp Sgl 75mg 10 (N1)	3
GE244517	Ben U Ron (B.A)Alt Tabl 500mg 10 (N1)	375
GE51137	Ben U Ron (B.A)Alt Tabl 500mg 20 (N2)	1131
GE1533750	Ben U Ron (B.A)Alt Tabl 500mg 200	3
GE184486	Ben U Ron (B.A)Alt Tabl 500mg 50 (N3)	109
GE11170083	Ben-U-Ron (G-O) Gr.Di.Er.Va. 250mg 10 (N1)	1
GE11113400	Ben-U-Ron (G-O) Gr.Di.Er.Va. 250mg 20 (N2)	1
GE12261382	Ben-U-Ron (G-O) Gr.Di.Er.Va. 500mg 10 (N1)	5
GE11022102	Ben-U-Ron (G-O) Gra.Dir.Capp 1000mg 10 (N1)	5
GE11017363	Ben-U-Ron (G-O) Gra.Dir.Capp 500mg 10 (N1)	2
GE11574490	Ben-U-Ron (G-O) Gra.Dir.Capp 500mg 20 (N2)	6
GE3881	Ben-U-Ron (G-O) Hartkapseln 500mg 10 (N1)	22
GE3882	Ben-U-Ron (G-O) Hartkapseln 500mg 20 (N2)	302
GE251794	Ben-U-Ron (G-O) Hartkapseln 500mg 200	8
GE6529913	Ben-U-Ron (G-O) Hartkapseln 500mg 50 (N3)	128
GE11055362	Ben-U-Ron (G-O) Supp Comfort 125mg Kdr 10 (N1)	1
GE11960561	Ben-U-Ron (G-O) Supp Comfort 75mg Sgl 10 (N1)	2
GE3889	Ben-U-Ron (G-O) Supp Erw 1000mg 10 (N1)	202
GE208416	Ben-U-Ron (G-O) Supp Erw 1000mg 100	27
GE3897	Ben-U-Ron (G-O) Supp Kleinkd 250mg 10 (N1)	7
GE3901	Ben-U-Ron (G-O) Supp Schulkd 500mg 10 (N1)	61
GE805542	Ben-U-Ron (G-O) Supp Schulkd 500mg 100	5
GE3900	Ben-U-Ron (G-O) Supp Schulkd 500mg 5 (N1)	1
GE3893	Ben-U-Ron (G-O) Supp Sgl 125mg 10 (N1)	6
GE4674432	Ben-U-Ron (G-O) Supp Sgl 75mg 10 (N1)	9

Therapy No.	Therapy Name	Count
GE10986235	Ben-U-Ron (G-O) Tabl Brause 1000mg 10 (N1)	9
GE6624533	Ben-U-Ron (G-O) Tabl 1000mg 18 (N2)	41
GE6540311	Ben-U-Ron (G-O) Tabl 1000mg 45	258
GE6578153	Ben-U-Ron (G-O) Tabl 1000mg 9 (N1)	114
GE3887	Ben-U-Ron (G-O) Tabl 500mg 10 (N1)	79
GE3888	Ben-U-Ron (G-O) Tabl 500mg 20 (N2)	630
GE34544	Ben-U-Ron (G-O) Tabl 500mg 200	33
GE4800027	Ben-U-Ron (G-O) Tabl 500mg 50 (N3)	543
GE9674625	Ben-U-Ron (G-O) Tabl Kva 500mg 200	1
GE142177	Captin Supp Kdr 500mg 10 (N1)	1
GE5361	Captin Tabl 500mg 10 (N1)	3
GE268061	Captin Tabl 500mg 30 (N2)	3
GE10126433	Docmorris Paracet. Schmerztabl 500mg 20 (N2)	33
GE115943	Doloreduct Supp 1g 10 (N1)	6
GE136021	Doloreduct Supp Kdr 125mg 10 (N1)	8
GE91923	Doloreduct Supp Kdr 500mg 10 (N1)	1
GE91924	Doloreduct Tabl 500mg 30 (N2)	324
GE121619	Dorocoff Paracetam Tabl 500mg 10 (N1)	1
GE409669	Dorocoff Paracetam Tabl 500mg 20 (N2)	41
GE682724	Dorocoff Paracetam Tabl 500mg 30 (N2)	3
GE366517	Dorocoff Paracetam Tabl 500mg 50 (N3)	18
GE59341	Duracetamol Tabl 500mg 10 (N1)	49
GE170093	Duracetamol Tabl 500mg 20 (N2)	8
GE16916944	Enelfa (Dol) Tabl 500mg 20 (N2)	1
GE10812	Enelfa (Did)Alt Supp Kdr 500mg 10 (N1)	1
GE10806	Enelfa (Did)Alt Tabl 500mg 10 (N1)	1
GE1138180	Enelfa (Did)Alt Tabl 500mg 20 (N2)	4
GE509288	Enelfa (Did)Alt Tabl 500mg 30 (N2)	1
GE399113	Fensum Supp Erw 1000mg 10 (N1)	7
GE340422	Fensum Supp Kdr 500mg 10 (N1)	1
GE160962	Fensum Tabl 500mg 10 (N1)	125
GE126010	Fensum Tabl 500mg 30 (N2)	248
GE9389710	Gib Paracetamo(Axe Tabl 500mg 20 (N2)	31
GE395557	Grippex Tabl 500mg 10 (N1)	1
GE342164	Grippex Tabl Brause 500mg 10 (N1)	36
GE852730	Julphar Dol Tabl 500mg 10 (N1)	16
GE505436	Julphar Dol Tabl 500mg 30 (N2)	27
GE17681371	Medpex Paracetamol Tabl 500mg 20 (N2)	5
GE19976	Mono Praecimed Supp Erw 1000mg 10 (N1)	2
GE19978	Mono Praecimed Supp Kdr 500mg 10 (N1)	2
GE168990	Mono Praecimed Tabl 500mg 30 (N2)	170
GE575175	Paedialgon Tabl 500mg 20 (N2)	1
GE7420223	Panadol Tabl Brause 500mg 12 (N2)	1

Therapy No.	Therapy Name	Count
GE15841993	Paracet Pcm Bene Tabl 1000mg 45	3
GE16452996	Paracet.Ipa/Apo-Ro Tabl 500mg 20 (N2)	593
GE16932377	Paracet.Ipa/Medpex Tabl 500mg 20 (N2)	9
GE988163	Paracetam. Wpa(Crs Tabl 500mg 20 (N2)	86
GE393051	Paracetam. Wpa(Crs Tabl 500mg 30 (N2)	429
GE17028103	Paracetam.Apog.Alt Tabl 500mg 20 (N2)	6
GE17024695	Paracetam.Buss.Gi. Tabl 500mg 20 (N2)	30
GE14912117	Paracetam.Elac Ipz Tabl 500mg 20 (N2)	176
GE8445144	Paracetam.Elac Tev Tabl 500mg 20 (N2)	462
GE16239416	Paracetam.Ipa/Dr.S Tabl 500mg 20 (N2)	2
GE16250905	Paracetam.Ipa/Mach Tabl 500mg 20 (N2)	5
GE16530814	Paracetam.Ipa/Medi Tabl 500mg 20 (N2)	7
GE8300568	Paracetamo.Sophien Tabl 500mg 20 (N2)	50
GE7488312	Paracetamo.Sophien Tabl 500mg 30	107
GE469619	Paracetamol Oh Tabl 500mg	1
GE228326	Paracetamol Azu Supp Erw 1000mg 10 (N1)	36
GE427429	Paracetamol Azu Supp Schulkd 500mg 10 (N1)	7
GE270097	Paracetamol Azu Tabl 500mg 30 (N2)	620
GE10834145	Paracetamol B.A Supp Eas Erw 1000mg 10 (N1)	15
GE11396567	Paracetamol B.A Supp Eas Erw 500mg 10 (N1)	27
GE14673568	Paracetamol B.T Tabl 500mg 20 (N2)	2447
GE17090900	Paracetamol F7d Tabl Apolif 500mg 20 (N2)	133
GE17225352	Paracetamol F7d Tabl 500mg 20 (N2)	28
GE17513188	Paracetamol F7d Tabl Avie 500mg 20 (N2)	7
GE10158879	Paracetamol F7d Tabl Disapo 500mg 20 (N2)	40
GE7617275	Paracetamol F7d Tabl Fair-M. 500mg 20 (N2)	2756
GE7548504	Paracetamol F7d Tabl Fair-M. 500mg 30 (N2)	109
GE17034975	Paracetamol F7d Tabl Klindw. 500mg 20 (N2)	21
GE17171066	Paracetamol F7d Tabl Medib. 500mg 20 (N2)	16
GE17369643	Paracetamol F7d Tabl Neu 500mg 20 (N2)	6
GE9942278	Paracetamol F7d Tabl Torrem 500mg 20 (N2)	19
GE16924711	Paracetamol Geh Schmerz.Bal 500mg 20 (N2)	1
GE15903849	Paracetamol Geh Schmerztabl 500mg 20 (N2)	12
GE417806	Paracetamol Ige Tabl 500mg 30 (N2)	117
GE2245458	Paracetamol Luh Tabl 500mg 30 (N2)	1
GE138999	Paracetamol Mip Supp Kdr 250mg 10 (N1)	1
GE139005	Paracetamol Mip Supp Kdr 250mg 5 (N1)	1
GE62919	Paracetamol Mip Tabl 500mg 10 (N1)	10
GE139001	Paracetamol Mip Tabl 500mg 20 (N2)	15
GE7542759	Paracetamol Mrh Tabl 500mg 20 (N2)	1289
GE729641	Paracetamol Mrh Tabl 500mg 30 (N2)	1926
GE86856	Paracetamol Psz Supp Erw 1000mg 10 (N1)	1
GE254285	Paracetamol Psz Supp Sgl 125mg 5 (N1)	1

Therapy No.	Therapy Name	Count
GE42111	Paracetamol Psz Tabl 500mg 10 (N1)	3
GE23331	Paracetamol Psz Tabl 500mg 20 (N2)	4
GE117043	Paracetamol Soh Kaps 500mg 10	4
GE1828182	Paracetamol Soh Kaps 500mg 20	1
GE62924	Paracetamol Soh Supp Erw 1000mg 10	73
GE3212691	Paracetamol Soh Supp Erw 1000mg 100	4
GE23946	Paracetamol Soh Supp Kdr 250mg 10	3
GE102395	Paracetamol Soh Supp Kdr 250mg 5	1
GE70722	Paracetamol Soh Supp Kdr 500mg 10	10
GE5537594	Paracetamol Soh Supp Kdr 500mg 100	2
GE101076	Paracetamol Soh Supp Kdr 500mg 5	3
GE146518	Paracetamol Soh Supp Sgl 125mg 10	1
GE501239	Paracetamol Soh Tabl 450mg 10	39
GE1579104	Paracetamol Soh Tabl 450mg 20	3
GE42122	Paracetamol Soh Tabl 500mg 10	636
GE1753452	Paracetamol Soh Tabl 500mg 100	61
GE1302509	Paracetamol Soh Tabl 500mg 1000	1
GE23320	Paracetamol Soh Tabl 500mg 20	2258
GE14332700	Paracetamol Soh Tabl 500mg 200	3
GE23311	Paracetamol Soh Tabl 500mg 30	251
GE3325584	Paracetamol Soh Tabl 500mg 300	3
GE91520	Paracetamol Soh Tabl 500mg 50	133
GE2379673	Paracetamol Soh Tabl 500mg 60	26
GE388377	Paracetamol Soh Tabl Brause 500mg 10	38
GE1471132	Paracetamol Soh Tabl Brause 500mg 20	2
GE637682	Paracetamol Tak Tabl 500mg 20 (N2)	7
GE10743582	Paracetamol Tgm Tabl 500mg 100	144
GE8578978	Paracetamol Volks Tabl 500mg 20	1362
GE6085455	Paracetamol Abz Supp Erw 1000mg 10 (N1)	332
GE5899427	Paracetamol Abz Supp Kdr 250mg 10 (N1)	19
GE6043459	Paracetamol Abz Supp Kdr 500mg 10 (N1)	244
GE5893545	Paracetamol Abz Supp Sgl 125mg 10 (N1)	22
GE6781679	Paracetamol Abz Tabl 500mg 10 (N1)	658
GE6814404	Paracetamol Abz Tabl 500mg 20 (N2)	8020
GE6689417	Paracetamol Abz Tabl 500mg 30 (N2)	410
GE9706904	Paracetamol Aiwa Tabl 500mg 20 (N2)	236
GE68386	Paracetamol Al Supp 125mg 10 (N1)	11
GE65047	Paracetamol Al Supp 250mg 10 (N1)	16
GE111655	Paracetamol Al Supp 500mg 10 (N1)	332
GE533548	Paracetamol Al Supp Erw 1000mg 10 (N1)	1336
GE3026678	Paracetamol Al Tabl 500mg 20 (N2)	12523
GE23291	Paracetamol Al Tabl 500mg 30 (N2)	8048
GE1716807	Paracetamol Ap Supp 1000mg 10 (N1)	4

Therapy No.	Therapy Name	Count
GE14297087	Paracetamol Apo-Ro Filmtabl 500mg 20 (N2)	165
GE7986133	Paracetamol Axcoun Tabl 500mg 20 (N2)	62
GE6827026	Paracetamol Axcoun Tabl 500mg 30 (N2)	28
GE340343	Paracetamol Basics Tabl 500mg 10 (N1)	1
GE11045461	Paracetamol Basics Tabl 500mg 20 (N2)	1360
GE526251	Paracetamol Basics Tabl 500mg 30 (N2)	2
GE1646657	Paracetamol Bc Supp Erw 1000mg 10 (N1)	117
GE253652	Paracetamol Bc Supp Kdr 500mg 10 (N1)	25
GE11882	Paracetamol Bc Supp Kleinkd 250mg 10 (N1)	2
GE409063	Paracetamol Bc Supp Sgl 125mg 10 (N1)	2
GE7628947	Paracetamol Bc Tab.D.Zulass 500mg 20 (N2)	29
GE391666	Paracetamol Bc Tabl 500mg 10 (N1)	719
GE168538	Paracetamol Bc Tabl 500mg 20 (N2)	1458
GE463997	Paracetamol Bc Tabl 500mg 30 (N2)	176
GE15790849	Paracetamol Bene Tabl 1000mg 9 (N1)	17
GE100612	Paracetamol Beta Supp Kleinkd 250mg 10 (N1)	12
GE395127	Paracetamol Beta Tabl 500mg 10 (N1)	269
GE60731	Paracetamol Beta Tabl 500mg 20 (N2)	1135
GE43128	Paracetamol Beta Tabl 500mg 30 (N2)	1391
GE17579922	Paracetamol Dexcel Tabl 500mg 20 (N2)	1
GE8377992	Paracetamol Dura Tabl 500mg 10 (N1)	88
GE8430105	Paracetamol Dura Tabl 500mg 20 (N2)	2385
GE7408580	Paracetamol Hemoph Tabl 500mg 20 (N2)	23
GE4762482	Paracetamol Hemoph Tabl 500mg 30 (N2)	3
GE171950	Paracetamol Heum. Supp Erw 1000mg 10 (N1)	543
GE1512562	Paracetamol Heum. Supp Erw 1000mg 100	1
GE394747	Paracetamol Heum. Supp Kdr 125mg 10 (N1)	1
GE333875	Paracetamol Heum. Supp Kdr 250mg 10 (N1)	8
GE333877	Paracetamol Heum. Supp Kdr 500mg 10 (N1)	134
GE56029	Paracetamol Heum. Tabl 500mg 10 (N1)	5327
GE8282203	Paracetamol Heum. Tabl 500mg 20 (N2)	3607
GE1114	Paracetamol Heum. Tabl 500mg 30	10905
GE1451037	Paracetamol Heum. Tabl 500mg 300	11
GE7998	Paracetamol Hexal Supp Erw 1000mg 10 (N1)	2557
GE198649	Paracetamol Hexal Supp Kdr 125mg 10 (N1)	41
GE112314	Paracetamol Hexal Supp Kdr 250mg 10 (N1)	63
GE280651	Paracetamol Hexal Supp Kdr 500mg 10 (N1)	997
GE7270111	Paracetamol Hexal Tabl 500mg 20 (N2)	7412
GE15537	Paracetamol Hexal Tabl 500mg 30 (N2)	13951
GE274004	Paracetamol Hexal Tabl Kva 500mg 30	269
GE16254645	Paracetamol Hormos Tabl 500mg 20 (N2)	3
GE15595534	Paracetamol Ipa Tabl 500mg 20 (N2)	50
GE15833033	Paracetamol Ipa/Ba Tabl 500mg 20 (N2)	7

Therapy No.	Therapy Name	Count
GE15945694	Paracetamol Ipa/Kl Tabl 500mg 20 (N2)	4
GE85403	Paracetamol L Lor Tabl 500mg 30 (N2)	46
GE281791	Paracetamol Opt Tabl 500mg 20 (N2)	13
GE5653248	Paracetamol Opt Tabl 500mg 500	6
GE213664	Paracetamol Pb(Pba Tabl 500mg 30 (N2)	8
GE2675536	Paracetamol Sandoz Supp Erw 1000mg 10 (N1)	140
GE100459	Paracetamol Sandoz Supp Schulkd 500mg 10 (N1)	41
GE2728391	Paracetamol Sandoz Supp Sgl 125mg 10 (N1)	2
GE7321062	Paracetamol Sandoz Tabl 500mg 10 (N1)	64
GE7351296	Paracetamol Sandoz Tabl 500mg 20 (N2)	623
GE357140	Paracetamol Sandoz Tabl 500mg 30 (N2)	1566
GE252842	Paracetamol Stada Supp Erw 1000mg 10 (N1)	647
GE5118	Paracetamol Stada Supp Kdr 250mg 10 (N1)	20
GE89046	Paracetamol Stada Supp Kdr 500mg 10 (N1)	224
GE86860	Paracetamol Stada Supp Sgl 125mg 10 (N1)	7
GE195040	Paracetamol Stada Tabl 250mg 20 (N2)	1
GE20372	Paracetamol Stada Tabl 500mg 10 (N1)	2158
GE7052947	Paracetamol Stada Tabl 500mg 20 (N2)	3254
GE140675	Paracetamol Stada Tabl 500mg 30	10508
GE11280874	Paracetamol Stada Tabl 500mg 50 (N3)	1944
GE15765327	Paracetamol Tad Tabl 500mg 20 (N2)	29
GE8498587	Paracetamol Teva Tabl 500mg 20 (N2)	40
GE16276375	Paracetamol Wepa Tabl 500mg 20 (N2)	17
GE7831616	Paracetamol-1a Ph. Supp 1000mg 10 (N1)	89
GE8401873	Paracetamol-1a Ph. Supp 500mg 10 (N1)	539
GE7813438	Paracetamol-1a Ph. Supp 500mg Alt 10 (N1)	8
GE8832741	Paracetamol-1a Ph. Supp Erw 1000mg 10 (N1)	2734
GE44090	Paracetamol-1a Ph. Supp Erw 1000mg Alt 10 (N1)	210
GE8278660	Paracetamol-1a Ph. Supp Kdr 125mg 10 (N1)	27
GE8327574	Paracetamol-1a Ph. Supp Kdr 250mg 10 (N1)	71
GE79631	Paracetamol-1a Ph. Supp Kleinkd 250mg 10 (N1)	10
GE243654	Paracetamol-1a Ph. Supp Schulkd 500mg 10 (N1)	21
GE248381	Paracetamol-1a Ph. Supp Sgl 125mg 10 (N1)	1
GE6632786	Paracetamol-1a Ph. Tabl 500mg 10 (N1)	10793
GE5418218	Paracetamol-1a Ph. Tabl 500mg 20 (N2)	68576
GE2669	Paracetamol-1a Ph. Tabl 500mg 30 (N2)	8526
GE8026591	Paracetamol-3a Ph. Tabl 500mg 20 (N2)	303
GE23314	Paracetamol-Ct Supp Erw 1g 10 (N1)	655
GE23318	Paracetamol-Ct Supp Kdr 250mg 10 (N1)	8
GE53417	Paracetamol-Ct Supp Kdr 500mg 10 (N1)	407
GE23317	Paracetamol-Ct Supp Sgl 125mg 10 (N1)	1
GE23293	Paracetamol-Ct Tabl 500mg 10 (N1)	3692
GE23313	Paracetamol-Ct Tabl 500mg 20 (N2)	15370

Therapy No.	Therapy Name	Count
GE2767	Paracetamol-Ct Tabl 500mg 30 (N2)	6399
GE10947172	Paracetamol-Ratiop Supp 75mg Sgl 10 (N1)	6
GE23301	Paracetamol-Ratiop Supp Erw 1g 10 (N1)	1994
GE23307	Paracetamol-Ratiop Supp Kdr 250mg 10 (N1)	28
GE23308	Paracetamol-Ratiop Supp Kdr 500mg 10 (N1)	245
GE23305	Paracetamol-Ratiop Supp Sgl 125mg 10 (N1)	13
GE99202	Paracetamol-Ratiop Tabl Brause 500mg 20 (N2)	1850
GE11367248	Paracetamol-Ratiop Tabl 1000mg 10 (N1)	386
GE10312348	Paracetamol-Ratiop Tabl 500mg 100	70
GE7189729	Paracetamol-Ratiop Tabl 500mg 20 (N2)	9035
GE23298	Paracetamol-Ratiop Tabl 500mg 30 (N2)	17445
GE334004	Paracetamol-Ratiop Tabl Brause 500mg 10 (N1)	549
GE11331208	Paracetamol-Ratiop Tablett.Box 500mg 20 (N2)	487
GE419077	Pcm H3p Tabl Brause 500mg 10 (N1)	17
GE572335	Pcm H3p Tabl Brause 500mg 20 (N2)	2
GE138996	Pcm Paracetamo.Zva Supp 1000mg 10 (N1)	68
GE145903	Pcm Paracetamo.Zva Supp Kdr 250mg 10 (N1)	6
GE94674	Pcm Paracetamo.Zva Supp Kdr 500mg 10 (N1)	64
GE160174	Pcm Paracetamo.Zva Supp Sgl 125mg 10 (N1)	1
GE343416	Pcm Paracetamo.Zva Tabl 500mg 20 (N2)	812
GE855761	Rubiemol Sa+ Supp Kdr 500mg 10 (N1)	2
GE144114	Rubiemol Sa+ Supp Sgl 125mg 10 (N1)	1
GE101820	Sinpro N (Bay) Tabl 500mg 50 (N3)	3
GE8080220	Tempil Paracetamol Tabl Hot 500mg 10 (N1)	2
GE2300333	Togal Paracetamol Supp Erw 1000mg 10 (N1)	1
GE140447	Treupel Mono Supp Kdr 500mg 10 (N1)	2
GE64632	Treupel Mono Tabl 500mg 20 (N2)	3
GE44784	Tylenol (J-C) Tabl 500mg 10 (N1)	1
GE522186	Vivimed N G.Fieber Tabl 500mg 10 (N1)	6
GE144238	Vivimed N G.Fieber Tabl 500mg 100	25
GE436851	Vivimed N G.Fieber Tabl 500mg 20 (N2)	86
GE240499	Vivimed N G.Fieber Tabl 500mg 60	43

Included paracetamol products in IMRD UK

drugcode	description	frequency
20228978	Paracetamol 500mg tablets	62
21286978	Paracetamol 500mg effervescent tablets sugar free	873
30021978	Paracetamol 500mg tablets	28
42691978	Paracetamol 500mg tablets	31
47264978	Paracetamol 500mg tablets	74
51975978	Paracetamol 500mg tablets	273
52674979	Paracetamol 500mg capsules	1
52678979	Paracetamol 500mg soluble tablets	39
52680979	Paracetamol 500mg tablets	334
61467979	Paracetamol 500mg capsules	1
70311978	Paracetamol 500mg tablets	547
72726978	Paracetamol 500mg tablets	191
73253978	Paracetamol 500mg tablets	311
76285978	Paracetamol 500mg tablets	1085
76286978	Paracetamol 500mg tablets	613
79802978	Paracetamol 500mg tablets	3992
82578978	Paracetamol 500mg tablets	622
82980998	Paracetamol 500mg soluble tablets	104
83324998	Paracetamol 500mg tablets	187
84357978	Paracetamol 500mg tablets	1231
89193998	Paracetamol 500mg tablets	108
89948998	Paracetamol 500mg tablets	1
90118998	Paracetamol 500mg soluble tablets	1
90264997	Paracetamol 500mg tablets	281
90264998	Paracetamol 500mg capsules	3
90290998	Paracetamol 500mg tablets	3
91585998	Paracetamol 500mg tablets	311
92042990	Paracetamol 500mg tablets	5
92269990	Paracetamol 500mg capsules	3
92701998	Paracetamol 500mg capsules	4
92995990	Paracetamol 500mg capsules	27
93556990	Paracetamol 500mg capsules	16
93925990	Paracetamol 500mg tablets	3975
93945992	Paracetamol 500mg soluble tablets	155
94475990	Paracetamol 500mg tablets	1424
94487990	Paracetamol 500mg capsules	73
94488990	Paracetamol 500mg soluble tablets	15
94686990	Paracetamol 500mg capsules	55
94689990	Paracetamol 500mg tablets	5
95030990	Paracetamol 500mg soluble tablets	26
95038990	Paracetamol 500mg tablets	281
95076990	Paracetamol 500mg tablets	39856
95104990	Paracetamol 500mg tablets	183516

95334998	Paracetamol 500mg tablets	309
95440990	Paracetamol 500mg soluble tablets	10
95468996	Paracetamol 500mg capsules	1957083
95468998	Paracetamol 500mg soluble tablets	1537321
95516990	Paracetamol 500mg tablets	3706
95576990	Paracetamol 500mg soluble tablets	138
95577990	Paracetamol 500mg capsules	16
95608990	Paracetamol 500mg soluble tablets	305
95747979	Paracetamol 500mg capsules	1
95750979	Paracetamol 500mg capsules	2
95753979	Paracetamol 500mg capsules	15
95755979	Paracetamol 500mg capsules	1
95756979	Paracetamol 500mg capsules	1
95782979	Paracetamol 500mg tablets	2134
95783979	Paracetamol 500mg tablets	19
95786979	Paracetamol 500mg tablets	1451
95788979	Paracetamol 500mg tablets	3591
95791979	Paracetamol 500mg tablets	738
95792979	Paracetamol 500mg tablets	16153
95793979	Paracetamol 500mg tablets	1
95794979	Paracetamol 500mg tablets	10914
95795979	Paracetamol 500mg tablets	4446
95796979	Paracetamol 500mg tablets	1
96105990	Paracetamol 500mg tablets	237
96106990	Paracetamol 500mg tablets	2578
96204990	Paracetamol 500mg tablets	11389
96204998	Paracetamol 500mg tablets	33
96290990	Paracetamol 500mg tablets	109
96417990	Paracetamol 500mg tablets	7
96565990	Paracetamol 500mg tablets	60
96572990	Paracetamol 500mg tablets	718
96940990	Paracetamol 500mg tablets	22458
97226998	Paracetamol 500mg tablets	24018057
97807998	Paracetamol 500mg tablets	610
97858992	Paracetamol 500mg soluble tablets	54366
97936990	Paracetamol 500mg tablets	86
97946989	Paracetamol 500mg tablets	207
98020990	Paracetamol 500mg capsules	46
98436990	Paracetamol 500mg tablets	5148
98467998	Paracetamol 500mg soluble tablets	241
98469997	Paracetamol 500mg capsules	808
98469998	Paracetamol 500mg tablets	335
98508989	Paracetamol 500mg capsules	84
98508990	Paracetamol 500mg tablets	706
98661989	Paracetamol 500mg tablets	2722
98741988	Paracetamol 500mg tablets	119

99139990	Paracetamol 500mg tablets	365
99140989	Paracetamol 500mg tablets	3
99141989	Paracetamol 500mg tablets	12549
99476988	Paracetamol 500mg capsules	376
99476989	Paracetamol 500mg soluble tablets	2070
99476990	Paracetamol 500mg tablets	4568
99477989	Paracetamol 500mg tablets	87

Appendix (5) Codes for identifying liver failure

Identification of patients with severe liver disease and possible liver failure in IMRD Germany

The ICD 10 codes K72 (Hepatic failure not elsewhere classified), K71.1 (Toxic liver disease with hepatic necrosis), K70.4 (Alcoholic hepatic failure) and B15-B19 (Viral hepatitis) were selected in order to identify patients with possible liver failure in IMRD Germany, excluding codes where the diagnosis was excluded or stated to be not confirmed (diagnostic certainty 'exclusion of' and 'not confirmed').

Identification of patients with chronic liver disease in IMRD UK

List of Chronic Liver Disease and Viral Hepatitis and Moderate or Severe Liver Disease (a subset of the former) taken from https://www.phpc.cam.ac.uk/pcu/cprd_cam/codelist/v11/ and derived from Khan et al (2010) Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Family Practice, doi: 10.1186/1471-2296-11-1

medcode	Read code	Description	Moderate or Severe Liver Disease
1638	J615z13	Cirrhosis of liver NOS	1
1641	G85..11	Oesophageal varices	1
1755	J614200	Chronic aggressive hepatitis	1
3450	J615300	Diffuse nodular cirrhosis	1
4743	J612.00	Alcoholic cirrhosis of liver	1
5129	J623.00	Portal hypertension	1
5638	J616000	Primary biliary cirrhosis	1
6015	Jyu7100	[X]Other and unspecified cirrhosis of liver	1
6863	J61..00	Cirrhosis and chronic liver disease	1
8206	C350012	Pigmentary cirrhosis of liver	1
8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver	1
9494	J616.00	Biliary cirrhosis	1
10636	J624.00	Hepatorenal syndrome	1
10797	G858.00	Oesophageal varices NOS	1
11960	760C300	Fibreoptic endoscopic injection sclerotherapy oesoph varices	1
15424	J616100	Secondary biliary cirrhosis	1
16455	J615z00	Non-alcoholic cirrhosis NOS	1
16725	J615.00	Cirrhosis - non alcoholic	1
16759	760C500	Fibreoptic endoscopic banding of oesophageal varices	1
17219	J635300	Toxic liver disease with chronic persistent hepatitis	1
18739	J615z12	Cryptogenic cirrhosis of liver	1
19512	C310400	Glycogenosis with hepatic cirrhosis	1
20233	7609z00	Open operation on oesophageal varices NOS	1
20912	7609400	Open injection sclerotherapy to oesophageal varices	1
22841	J615z11	Macronodular cirrhosis of liver	1
24220	7609.00	Open operations on oesophageal varices	1
24989	G850.00	Oesophageal varices with bleeding	1
26319	G852200	Oesophageal varices in cirrhosis of the liver	1
27438	J615700	Cardiac portal cirrhosis	1
28929	G857.00	Gastric varices	1
30655	G851.00	Oesophageal varices without bleeding	1
31897	J62..00	Liver abscess and sequelae of chronic liver disease	1
39351	J635500	Toxic liver disease with chronic active hepatitis	1
40567	J615600	Capsular portal cirrhosis	1
43404	7609300	Local ligation of oesophageal varices	1
44120	J635600	Toxic liver disease with fibrosis and cirrhosis of liver	1
44424	G852.00	Oesophageal varices in diseases EC	1
44676	J615400	Fatty portal cirrhosis	1
46647	760F400	Rigid oesophagoscopy banding of oesophageal varices	1
47214	760F300	Rigid oesophagoscopy injection sclerotherapy oesoph varices	1
47257	J615.11	Portal cirrhosis	1

medcode	Read code	Description	Moderate or Severe Liver Disease
48102	J62y.00	Other sequelae of chronic liver disease	1
48928	J615H00	Infectious cirrhosis NOS	1
55454	J615y00	Portal cirrhosis unspecified	1
58184	J615812	Indian childhood cirrhosis	1
58630	J616z00	Biliary cirrhosis NOS	1
62582	G852z00	Oesophageal varices in diseases EC NOS	1
64750	J635400	Toxic liver disease with chronic lobular hepatitis	1
65050	A704000	Viral hepatitis C with coma	1
68376	J612.11	Florid cirrhosis	1
69053	A702.00	Viral hepatitis B with coma	1
69204	J615100	Multilobular portal cirrhosis	1
73139	G852100	Oesophageal varices without bleeding in diseases EC	1
73482	J615D00	Bacterial portal cirrhosis	1
91591	J616200	Biliary cirrhosis of children	1
92909	J615500	Hypertrophic portal cirrhosis	1
96664	J615800	Juvenile portal cirrhosis	1
96756	G852000	Oesophageal varices with bleeding in diseases EC	1
100253	J615C00	Xanthomatous portal cirrhosis	1
100474	J612.12	Laennec's cirrhosis	1
102922	C370800	Cystic fibrosis related cirrhosis	1
105611	Gyu9400	[X]Oesophageal varices in diseases classified elsewhere	1
108800	J62z.00	Liver abscess and chronic liver disease causing sequelae NOS	1

Appendix (6) Paracetamol dose by age, sex & year of prescribing

IMRD Germany

Figure 3 Mean calculated daily doses of paracetamol in GP patients 45 years or older, stratified by gender and age group in IMRD Germany

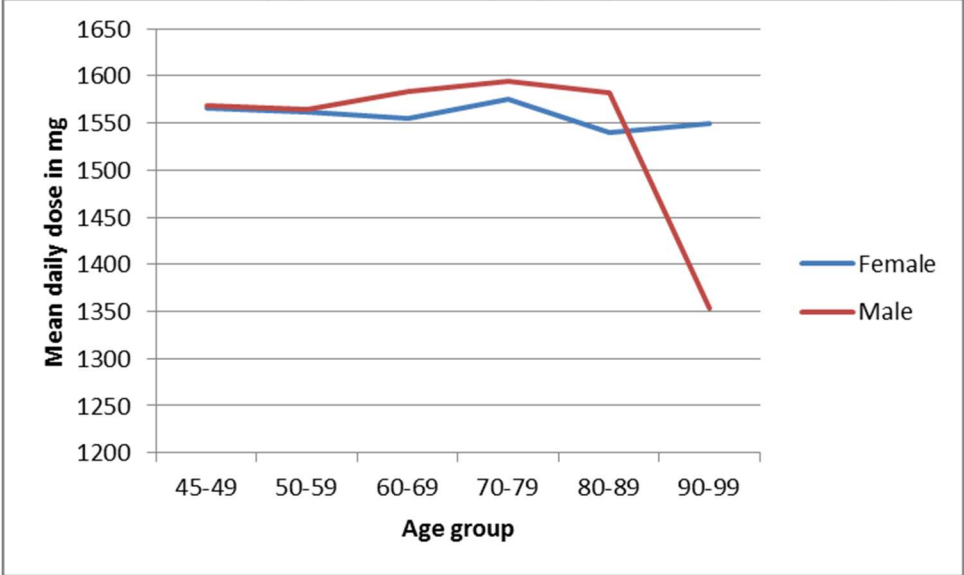


Figure 4 Mean calculated daily doses of paracetamol in GP patients 45 years or older by calendar year in IMRD Germany

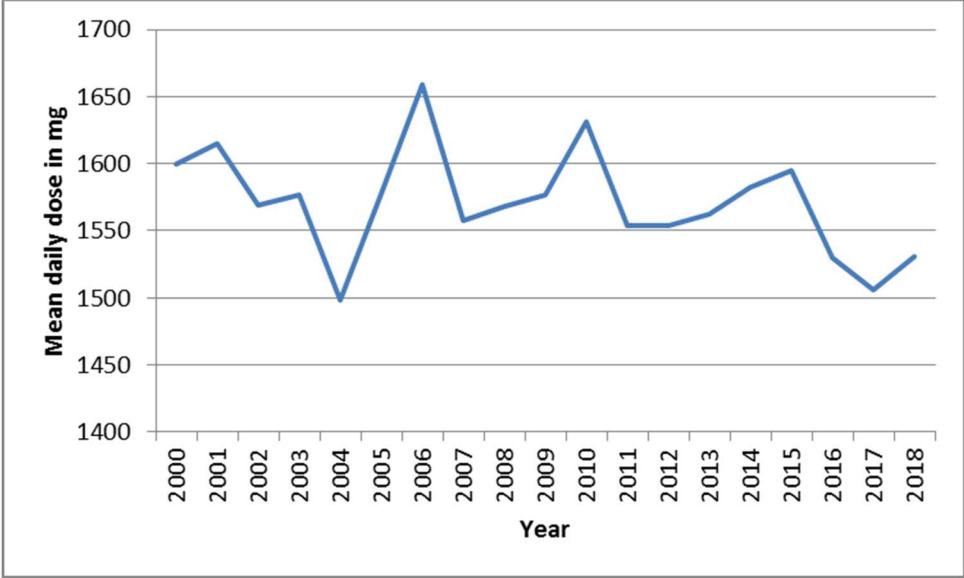


Figure 1 Mean calculated daily doses of paracetamol in GP patients 45 years or older, stratified by gender and age group in IMRD UK

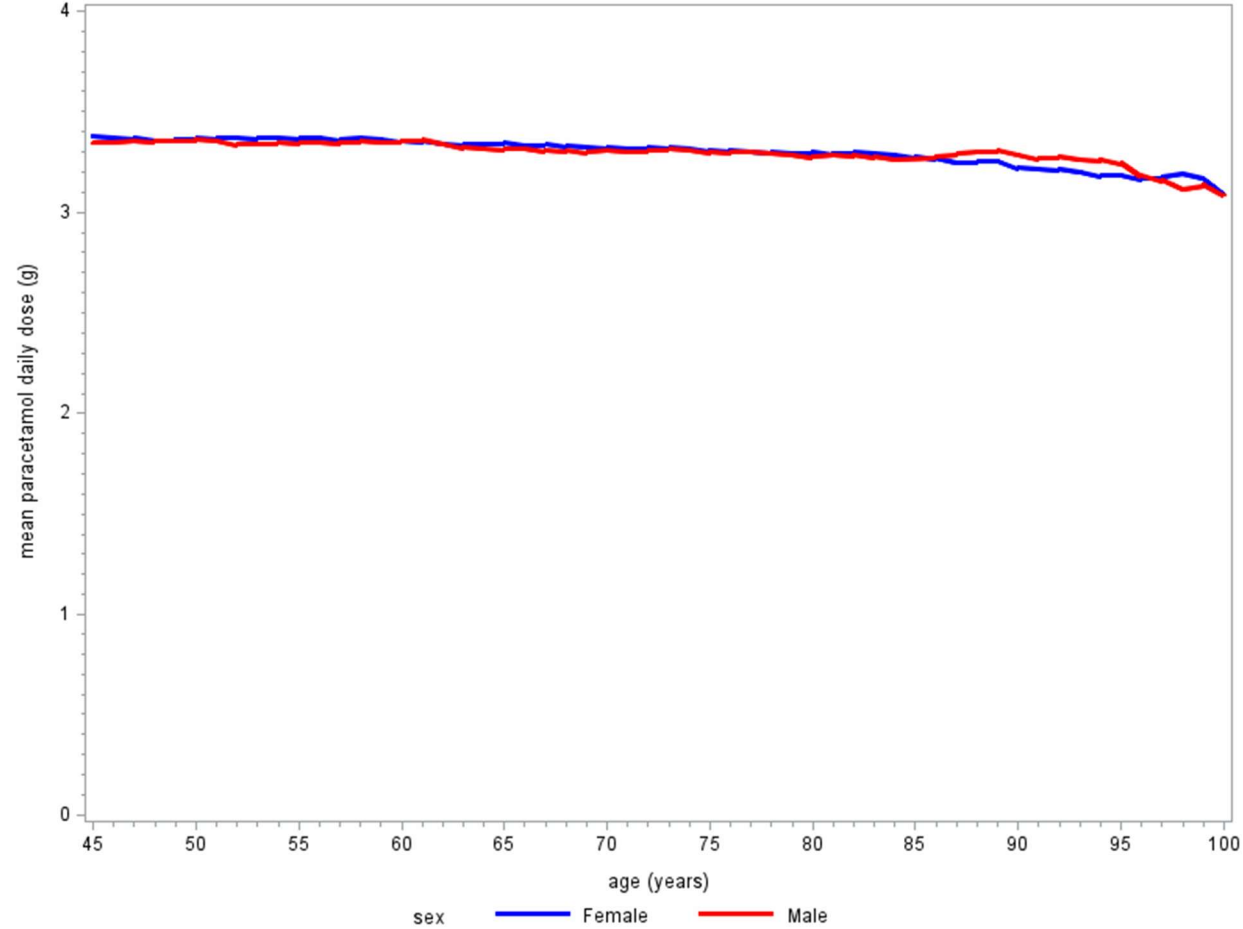
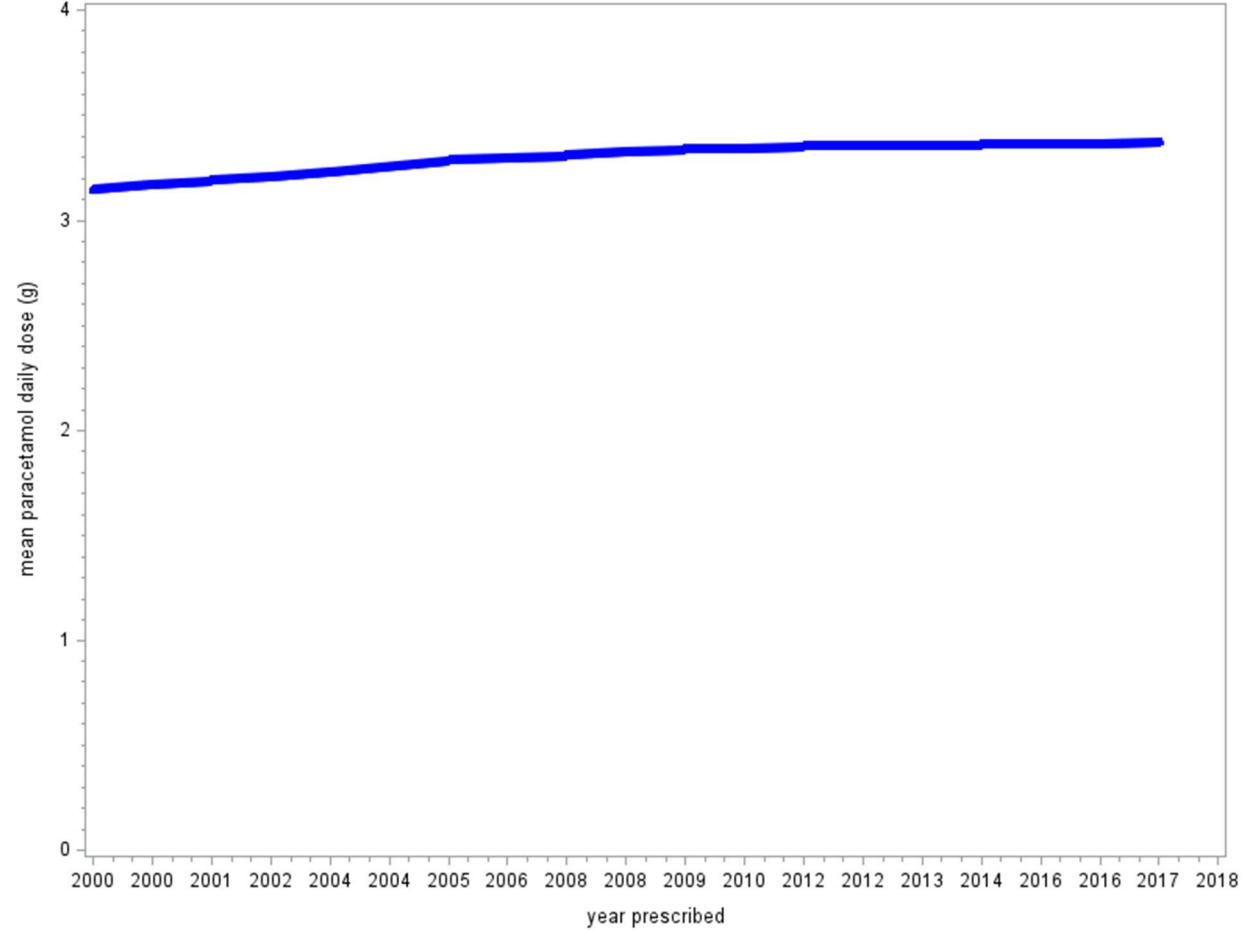


Figure 2 Mean calculated daily doses of paracetamol in GP patients 45 years or older by calendar year in IMRD UK



Appendix (7) Paracetamol dose by age, sex & year of prescribing in renal failure

IMRD Germany

Figure 5 Mean calculated daily doses of paracetamol in GP patients 45 years or older with renal failure, stratified by gender and age group in IMRD Germany

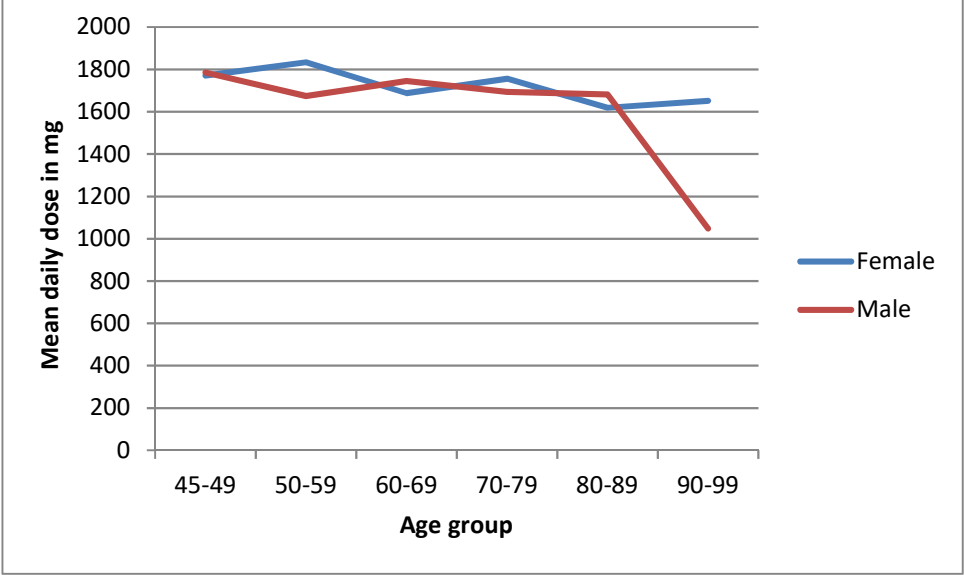
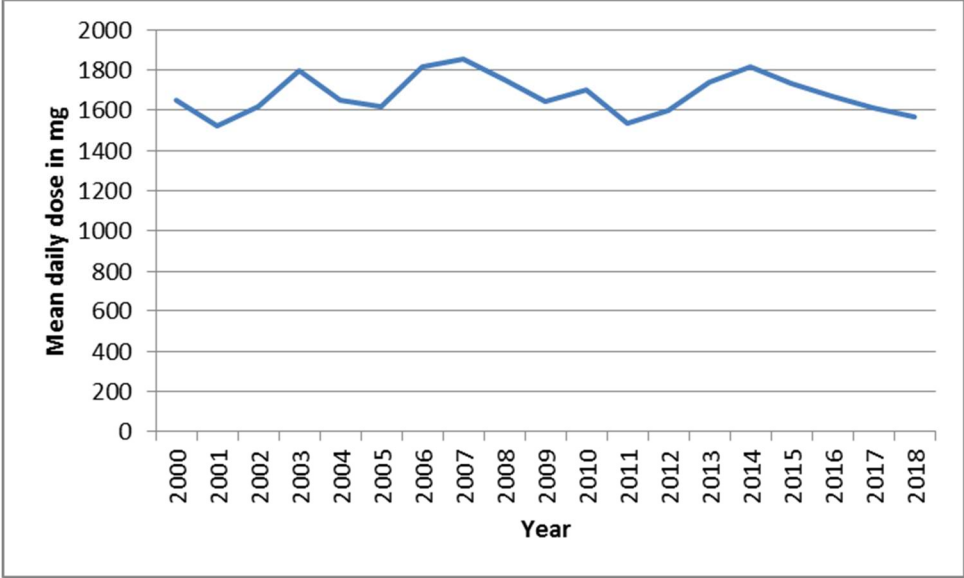


Figure 6 Mean calculated daily doses of paracetamol in GP patients 45 years or older with renal failure by calendar year in IMRD Germany



IMRD UK

Figure 3 Mean calculated daily doses of paracetamol in GP patients 45 years or older with renal failure, stratified by gender and age group in IMRD UK

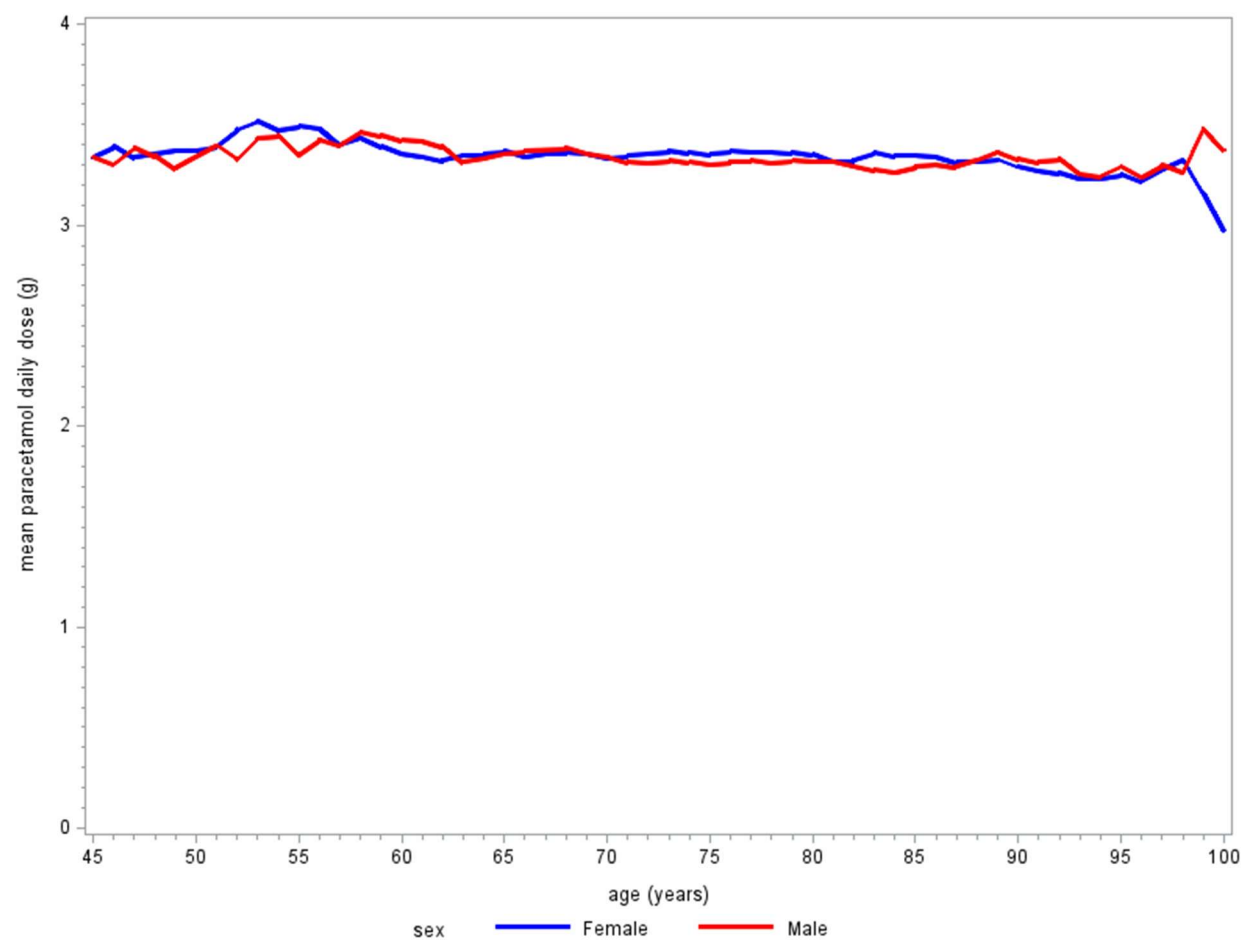
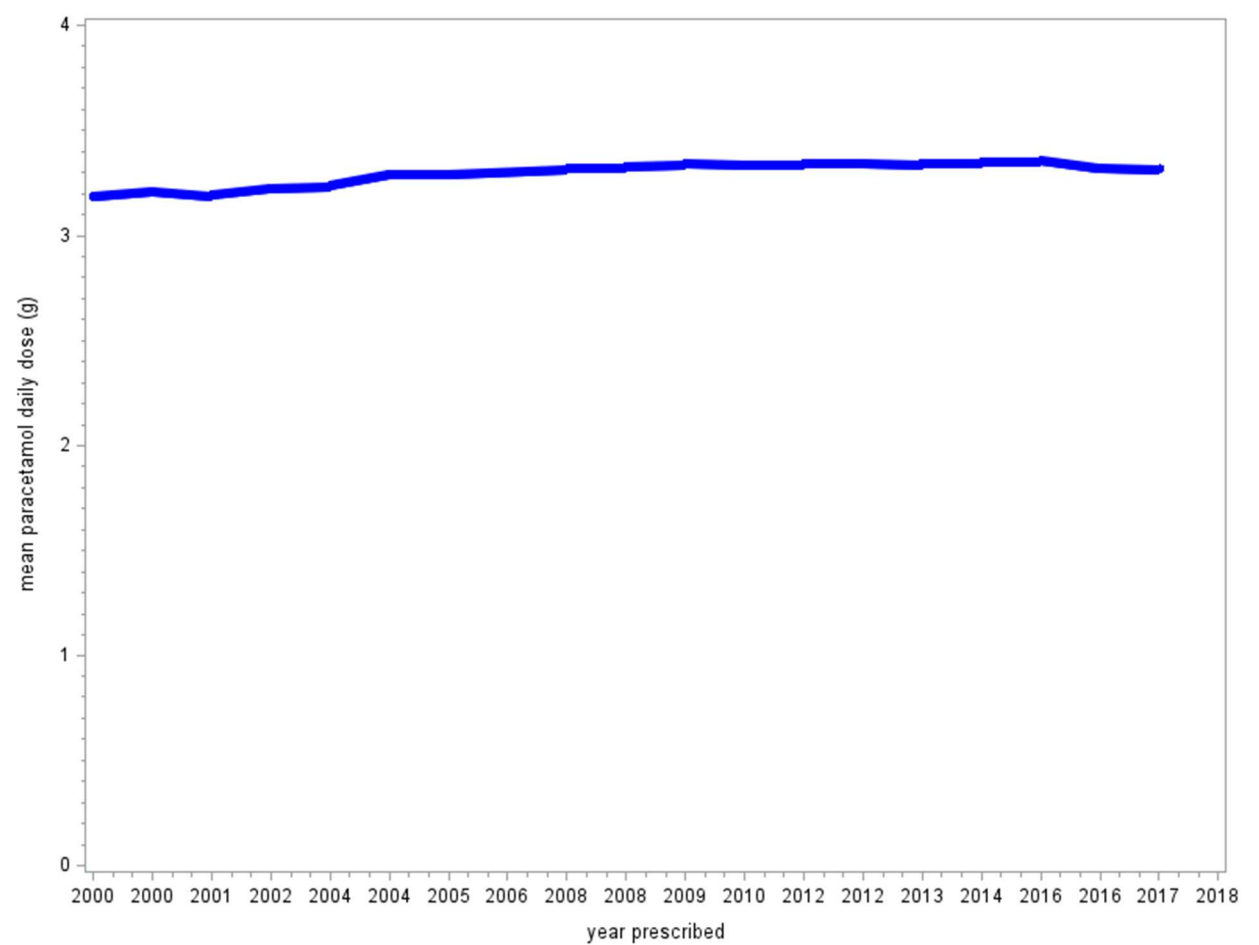


Figure 4 Mean calculated daily doses of paracetamol in GP patients 45 years or older with renal failure by calendar year in IMRD UK



Appendix (8) Dose by age, sex & year of prescribing without renal failure

IMRD Germany

Figure 7 Mean calculated daily doses of paracetamol in GP patients 45 years or older without renal failure, stratified by gender and age group in IMRD Germany

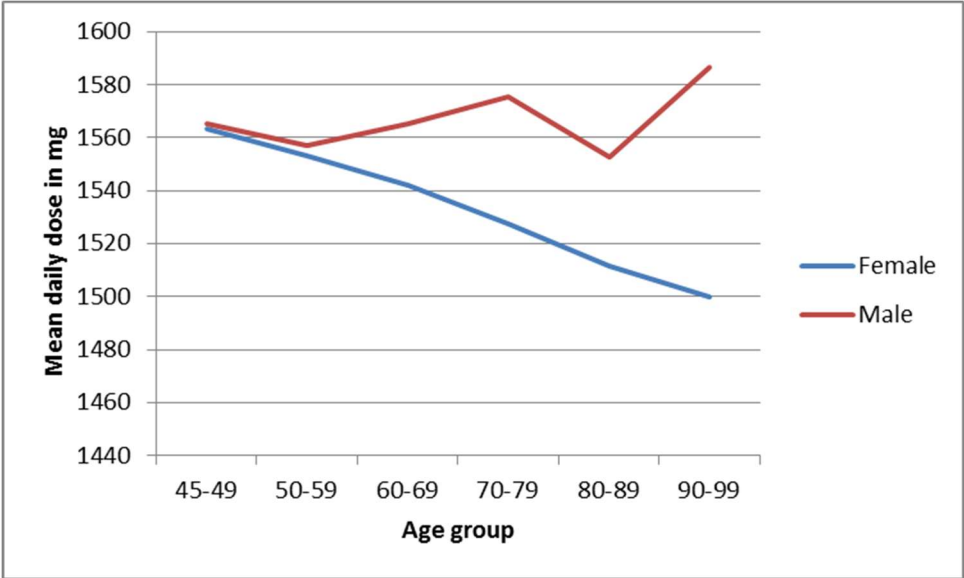


Figure 8 Mean calculated daily doses of paracetamol in GP patients 45 years or older without renal failure by calendar year in IMRD Germany

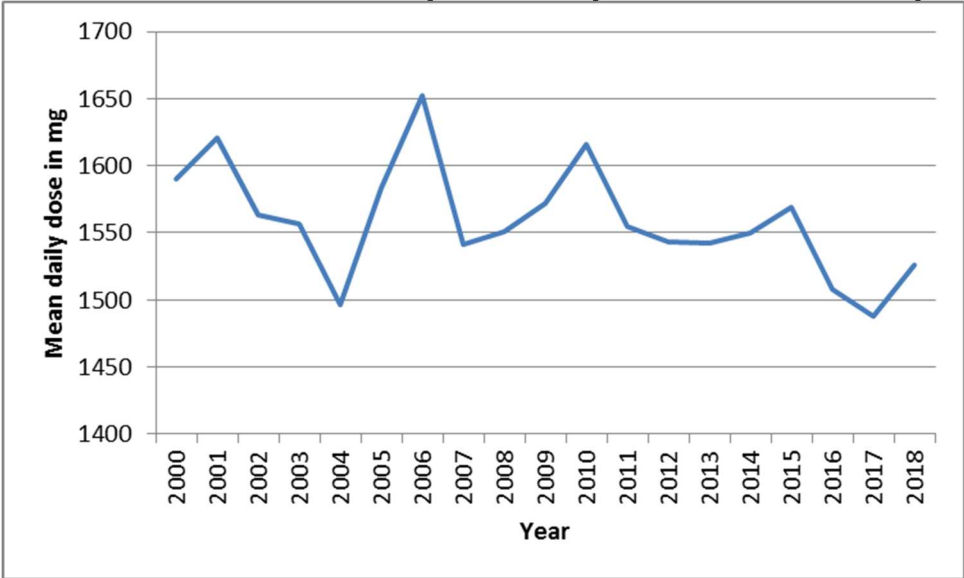


Figure 1 Mean calculated daily doses of paracetamol in GP patients 45 years or older without renal failure, stratified by gender and age group in IMRD UK

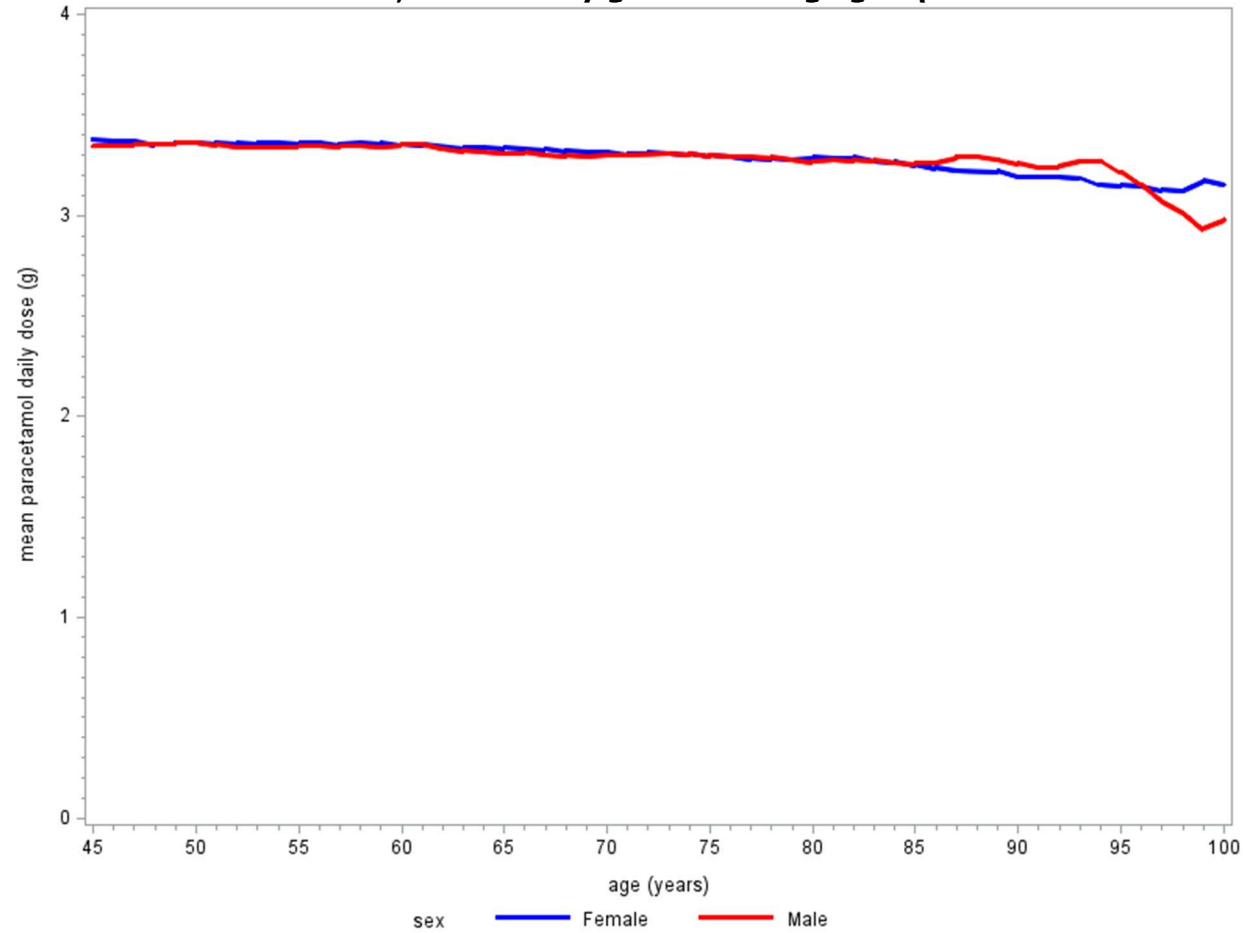
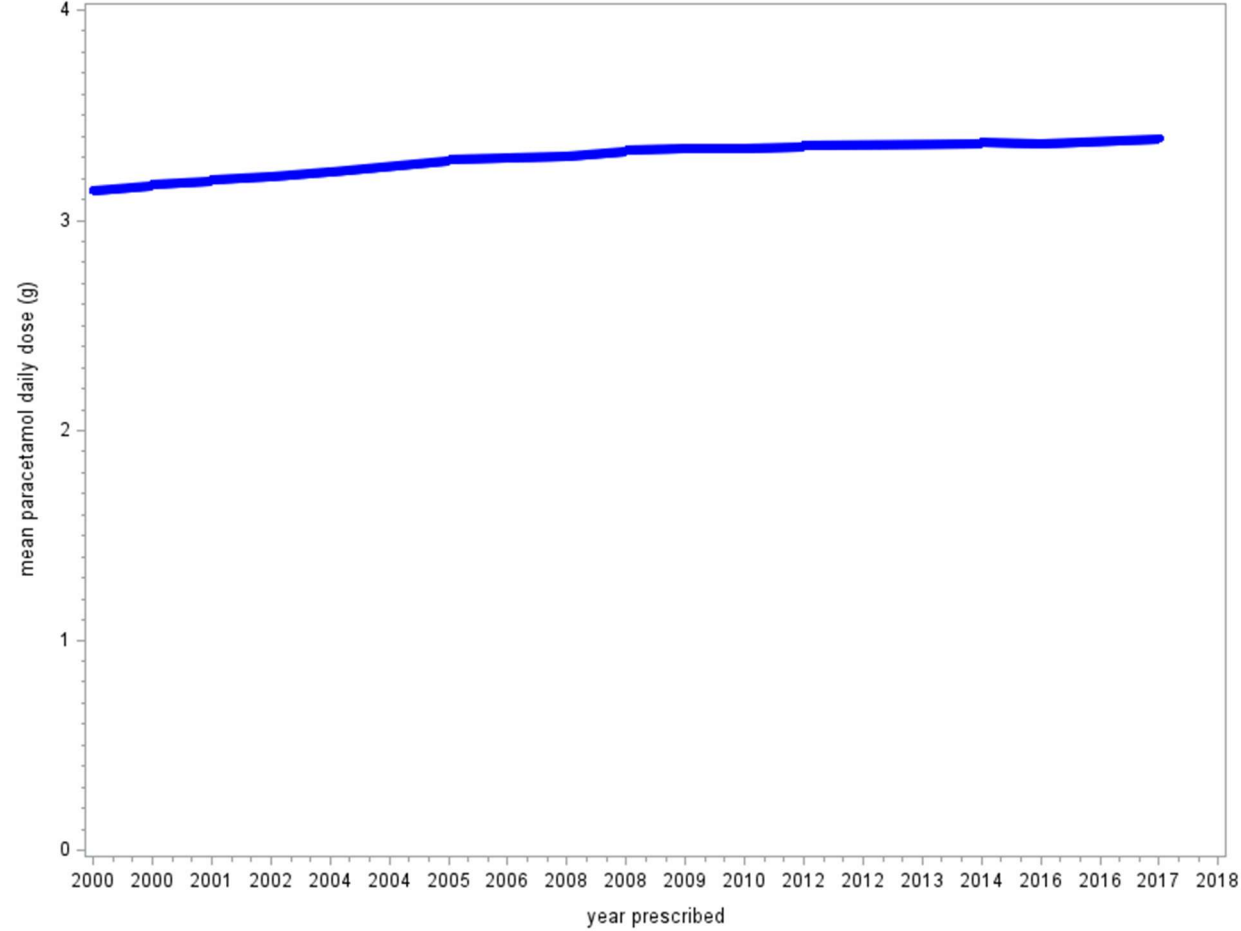


Figure 2 Mean calculated daily doses of paracetamol in GP patients 45 years or older without renal failure by calendar year in IMRD UK



Appendix (9) Matched analysis Germany

Table 1. Mean daily and total paracetamol doses in paracetamol prescriptions in patients with renal failure vs. patients without renal failure, restricted to practices that recorded at least 10% of paracetamol doses (445 out of 1238 GP practices)

	Patients with renal failure	Patients without renal failure
Mean daily dose (SD)	1683.6 mg (685.0 mg)	1548.7 mg (607.6 mg)
Median daily dose (IQR)	1500 mg (1500-2000 mg)	1500 (1000-1500)
Mean total dose (SD)	13,489.9 mg (8793.0 mg)	11,664.2 mg (5871.2 mg)
Median total dose (IQR)	10,000 mg (10,000-15,000 mg)	10,000 mg (10,000-15,000 mg)
No. of presc with DD = 4 g	102 (2.4%)	333 (0.7%)
No. of presc with DD >2-<4 g	480 (11.3%)	5130 (10.8%)
No. of presc with DD ≤2 g	3663 (86.3%)	41,854 (88.5%)

DD = daily dose, g = gram, GP = general practitioner, IQR = interquartile range, mg = milligram, presc = prescription, SD = standard deviation

A total of 12,189 paracetamol prescriptions in patients with renal failure concerned practices that recorded at least 10% of paracetamol doses. A dose was recorded in 4245 prescriptions.

A total of 113,030 paracetamol prescriptions in patients without renal failure concerned practices that recorded at least 10% of paracetamol doses. A dose was recorded in 47,317 prescriptions.

Table 2. Mean daily and total paracetamol doses in paracetamol prescriptions in patients with renal failure vs. patients without renal failure, matched 1:1 on gender, age and year of prescription

	Patients with renal failure (3261 prescriptions)	Patients without renal failure (3261 prescriptions)
Mean daily dose (SD)	1688.4 mg (691.0 mg)	1549.2 mg (630.6 mg)
Median daily dose (IQR)	1500 mg (1500-2000 mg)	1500 mg (1000-1500 mg)
Mean total dose (SD)	13,639.3 mg (10,071.0 mg)	12,923.8 mg (8843.3 mg)
Median total dose (IQR)	10,000 mg (10,000-15,000 mg)	10,000 mg (10,000-15,000 mg)
No. of presc with DD = 4 g	85 (2.6%)	26 (0.8%)
No. of presc with DD >2-<4 g	375 (11.5%)	335 (10.3%)
No. of presc with DD ≤2 g	2801 (85.9%)	2900 (88.9%)

DD = daily dose, g = gram, IQR = interquartile range, mg = milligram, presc = prescription, SD = standard deviation

Table 3. Mean daily and total paracetamol doses in paracetamol prescriptions in patients with renal failure vs. patients without renal failure, excluding patients with prior liver failure

	Patients with renal failure	Patients without renal failure
Mean daily dose (SD)	1674.3 mg (685.3 mg)	1549.8 mg (615.0 mg)
Median daily dose (IQR)	1500 mg (1500-2000 mg)	1500 (1000-1500)
Mean total dose (SD)	12,785.0 mg (7843.8 mg)	11,677.7 mg (6013.4 mg)
Median total dose (IQR)	10,000 mg (10,000-15,000 mg)	10,000 mg (10,000-15,000 mg)
No. of presc with DD = 4 g	111 (2.4%)	378 (0.8%)
No. of presc with DD >2-<4 g	514 (10.9%)	5449 (10.9%)
No. of presc with DD ≤2 g	4090 (86.7%)	44,283 (88.4%)

DD = daily dose, g = gram, IQR = interquartile range, mg = milligram, presc = prescription, SD = standard deviation

A total of 23,559 paracetamol prescriptions in patients with renal failure had no prior ICD 10 code for liver failure. A dose was recorded in 4715 prescriptions.

A total of 249,711 paracetamol prescriptions in patients without renal failure had no prior ICD 10 code for liver failure. A dose was recorded in 50,110 prescriptions.

ICD 10 codes for prior liver failure included K72 (Hepatic failure not elsewhere classified), K70.4 (Alcoholic hepatic failure), K71.1 (Toxic liver disease with hepatic necrosis), and B15-B19 (Viral hepatitis).