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REVIEW ARTICLE

Paracetamol in Older People: Towards Evidence-Based Dosing?

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Abstract

Paracetamol is the most commonly used analgesic in older people, and is mainly dosed according to empirical dosing guidelines. However, the pharmacokinetics and thereby the effects of paracetamol can be influenced by physiological changes occurring with ageing. To investigate the steps needed to reach more evidence-based paracetamol dosing regimens in older people, we applied the concepts used in the paediatric study decision tree. A search was performed to retrieve studies on paracetamol pharmacokinetics and safety in older people (> 60 years) or studies that performed a (sub) analysis of pharmacokinetics and/or safety in older people. Of 6088 articles identified, 259 articles were retained after title and abstract screening. Further abstract and full-text screening identified 27 studies, of which 20 described pharmacokinetics and seven safety. These studies revealed no changes in absorption with ageing. A decreased (3.9–22.9%) volume of distribution (V_d) in robust older subjects and a further decreased V_d (20.3%) in frail older compared with younger subjects was apparent. Like V_d, age and frailty decreased paracetamol clearance (29–45.7 and 37.5%) compared with younger subjects. Due to limited and heterogeneous evidence, it was difficult to draw firm and meaningful conclusions on changed risk for paracetamol safety in older people. This review is a first step towards bridging knowledge gaps to move to evidence-based paracetamol dosing in older subjects. Remaining knowledge gaps are safety when using therapeutic dosages, pharmacokinetics changes in frail older people, and to what extent changes in paracetamol pharmacokinetics should lead to a change in dosage in frail and robust older people.

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Key Points

Paracetamol is the most commonly used analgesic in older people, and is mainly dosed according to clinical experience, expert opinions or extrapolated from studies in younger adults. However, physiological changes occur with increasing age and can thereby influence the pharmacokinetics and effect of paracetamol.

Based on different non-compartmental pharmacokinetic paracetamol studies, decreases in clearance (CL) and volume of distribution (V_d) between young adults and robust older subjects have been reported, with further decreases of CL and V_d in frail older people. Consequently, the question should no longer be if these changes are statistically significant, but whether the difference in pharmacokinetic parameters in older subjects is clinically relevant enough for dose adaptation.

Based on the—albeit limited—observations retrieved in our search, there is no evidence to support a higher incidence of hepatotoxicity of paracetamol in normal dosages in older subjects. Overall, due to limited and heterogeneous evidence, it was difficult to draw firm and meaningful conclusions on changed risk for paracetamol safety in older people.

Remaining knowledge gaps are safety when using therapeutic dosages, pharmacokinetic changes in frail older people, and to what extent the changes in paracetamol pharmacokinetics should lead to an adaptation in dosing in both frail and robust older people.

1 Introduction

Worldwide, 901 million people were aged 60 years or older in 2015 [1]. This older population has increased by 48% from 2000 and will continue to increase [2]. Obviously, diseases become more prevalent with advanced age and with them the use of multiple medications [2, 3]. The use of medication by older people has increased 3- to 5-fold over the past decades and is expected to rise even more [4].

Pain (mostly chronic) is one of the most common problems among older people and a very common indication for pharmacotherapy [5, 6]. As older people undergo surgery four times more often than younger populations [7], they arguably also have a larger probability of acute pain. Thus, effective pain management is obviously needed [8]. Unfortunately, older people's pain is often underreported, underestimated and undertreated [9]. Ineffective management is partly caused by older people's changed physiology; that is, increased total body fat and decreased kidney function [10, 11]. Furthermore, drug dosing is often inappropriate because older people (including those with multiple comorbidities) are hardly ever included in clinical trials [10, 12]. Several guidelines and consensus papers have been written to overcome this problem, but these are mostly based on clinical experience, expert opinions and current treatment extrapolated from studies in younger adults [9].

Paracetamol (acetaminophen, APAP) is the most used analgesic in older people; for example, to treat musculoskeletal or low back pain [12]. Paracetamol is extensively metabolised by different pathways in the liver (Fig. 1) [13]. In young adults, paracetamol is metabolised to paracetamol-glucuronide and paracetamol-sulphate as main metabolites (85–90%) [14–16]. Five percent is excreted as unchanged paracetamol in urine and 5–10% is oxidised by cytochrome P450 (CYP450), primarily by CYP2E1, to a toxic metabolite, N-acetyl-p-benzoquinone-imine (NAPQI) [17]. At therapeutic doses, NAPQI is subsequently neutralised by glutathione and is excreted as cysteine and mercapturate metabolites by the renal route. However, glutathione can be depleted, such as in case of an overdose or malnourished state, resulting in acute liver damage [18, 19].

Although several guidelines provide dosing advice (Table 1), there is no specific focus on older people, either robust or frail, and with or without comorbidity. The physiological changes associated with ageing potentially influences the pharmacokinetics of paracetamol and thereby its effects [20]. Furthermore, to have a better evidence base for dosing, safety should be considered given the potential

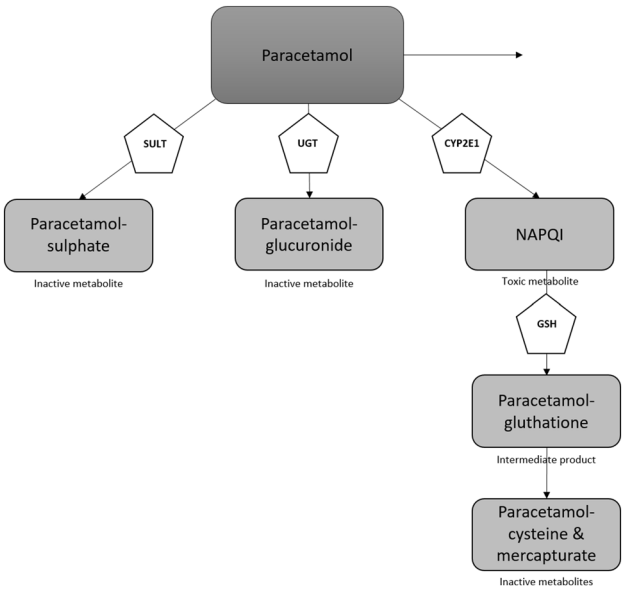

Fig. 1 Overview of paracetamol metabolism. *CYP2E1* cytochrome-P450 2, *GSH* glutathione, *NAPQI* *N*-acetyl-*p*-benzoquinone-imine, *SULT* sulphotransferase, *UGT* UDP-glucuronosyltransferase

Table 1 Dosing suggestions from guidelines and labels for paracetamol for older people

	Dosing advice	Maximum daily dose	Remark
Guideline or consensus			
American Geriatrics Society [62]	325–500 mg every 4 h or 500–1000 mg every 6 h	4000 mg	Reduce maximum dose 50–75% in patients with hepatic insufficiency or history of alcohol abuse
British Geriatrics Society [63]		4000 mg	
Labels for intravenous administration			
OFIRMEV (USA) [64]			
Adults ≥ 50 kg	1000 mg every 6 h or 650 mg every 4 h	4000 mg	
Adults < 50 kg	15 mg/kg every 6 h or 12 mg/kg every 4 h	75 mg/kg	
Perfalgan (EU) [65]			
Adults > 50 kg	1000 mg Minimum interval between each administration must be at least 4 h	4000 mg	Minimal interval between each administration must be at least 6 h for patients with severe renal insufficiency No more than 4 doses to be given in 24 h Maximum daily dose is 3000 mg for patients > 50 kg with additional risk factors for hepatotoxicity
Adults ≤ 50 kg	15 mg/kg	60 mg/kg not exceeding 3000 mg	
Labels for oral administration			
Tylenol® (USA)			
Adults	1000 mg every 6 h	3000 mg	
Panadol® (EU) [66]			
Adults > 15 years of age and > 55 kg	500–1000 mg, every 4–6 h	3000 mg	
Adults ≤ 55 kg	500 mg, every 4–6 h	3000 mg	

USA United States of America, *EU* European Union

toxicity of one of the metabolites. Therefore, for this special population, the key question is *what dose should we consider as optimal?*

For the paediatric population, the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) proposed a study decision tree to guide drug development and to generate evidence-based dosing [21, 22]. This decision tree can also be applied in other special populations in which physiological changes [20] occur, such as older people. This paediatric study decision tree consists of an assumption-based framework to determine the type of information needed for labelling, or to support more evidence-based dosing of existing drugs [21, 22]. It enables extrapolation of efficacy, from (healthy) young adult data or data in other subpopulations. The assumptions to be considered are similarity in disease progression, response to intervention and exposure–response relationships in the paediatric population and adults. Pharmacokinetics, pharmacodynamics and/or safety studies have to be conducted, taking into account the presence or absence of these similarities [21, 22].

When applying this study decision tree in both robust and frail older people (Fig. 2), it seems reasonable to assume similarities in pain (e.g. postoperative, traumatic, chronic) relief response between younger adults and older people following similar paracetamol exposure. This is, however, an assumption not yet supported by robust data. Based on this decision tree, pharmacokinetics and safety studies are pivotal to reach safe and effective analgesic use of paracetamol in both robust and frail older people (Fig. 2 grey boxes). Applying this study decision tree in older people minimises the exposure of older people in clinical trials and facilitates more timely access to effective and safe medicines, or at least pharmacokinetics and factors influencing pharmacokinetics (e.g. covariates) are a prerequisite to explore potential age-dependent differences in pain relief response following paracetamol exposure.

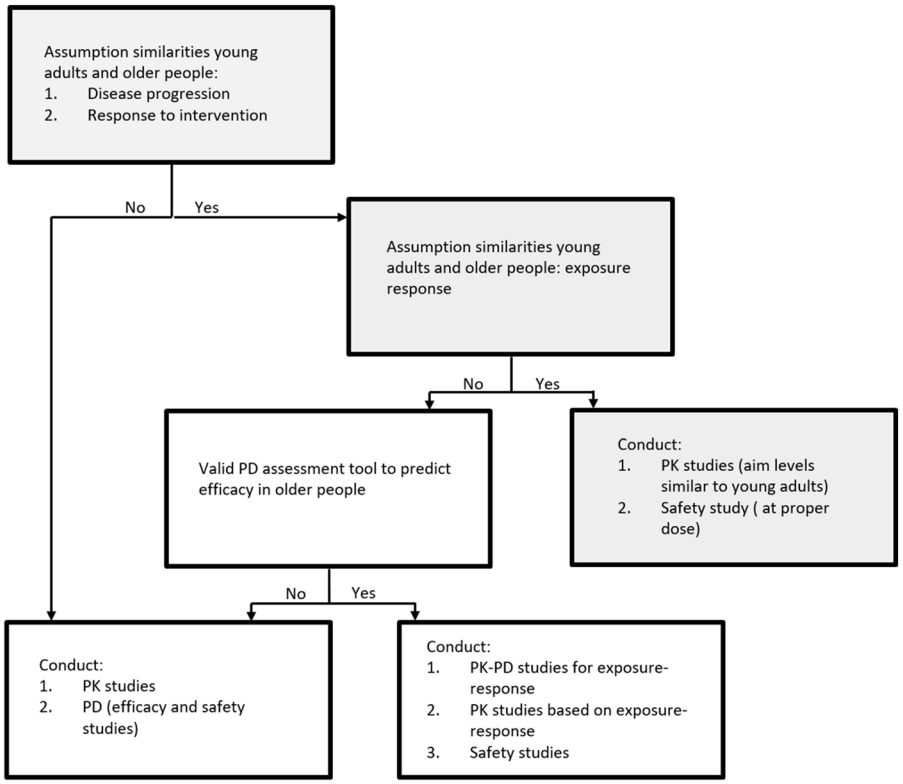

Fig. 2 Paediatric study decision tree [21, 22] applied to paracetamol in older people (grey boxes apply). *PD* pharmacodynamics, *PK* pharmacokinetics

In this review, we applied the study decision tree using paracetamol in (a) robust older people and (b) geriatric patients (i.e. with frailty, multi-morbidity, polypharmacy), and aimed to inventory what is already known of pharmacokinetics and safety. Our ultimate goal is to investigate which steps are needed to reach evidence-based dosing of paracetamol in this heterogeneous and growing population.

2 Methods

2.1 Inclusion Criteria

A search was performed to retrieve studies on paracetamol pharmacokinetics and safety in older people or studies that performed a sub-analysis of pharmacokinetics and safety in older people. Studies on both paracetamol and propacetamol were considered, as propacetamol (no longer marketed in Europe) is a prodrug of paracetamol that is rapidly hydrolysed (propacetamol 1 g to paracetamol 0.5 g) by plasma esterase [23]. Paracetamol by both intravenous and enteral (oral, rectal) routes of administration were considered for inclusion. Only studies including paracetamol in therapeutic dosages were included. Participants were both robust older people and geriatric patients (i.e. with frailty, multi-morbidity, polypharmacy). Older people included in the analysis were defined as those > 60 years of age [1]. To pinpoint the potential influence of ageing, studies comparing pharmacokinetics and/or safety of older people with that of younger subjects were included. The data of younger subjects were also extracted to enable comparison. However, we have not performed a fully systematic search on data in people < 60 years. Eligible studies were randomised controlled trials or observational studies.

2.2 Search Strategy

2.2.1 Electronic Resources

A search was conducted in Embase, Medline Ovid, Web of Science, Scopus, Cochrane Library, PubMed Publisher, CINAHL EBSCOhost and Google Scholar on 5 October 2017. No language restrictions were made. Keywords were paracetamol/acetaminophen/propacetamol, pharmacokinetics, pharmacodynamics, drug safety, elderly, frail, ageing. The search strategy is detailed in Appendix I (see electronic supplementary material [ESM]).

2.2.2 Other Resources

References of included studies were checked for relevant articles.

2.3 Study Selection and Data Extraction

Titles and abstracts of retrieved citations were screened for relevance by PM, after which full texts of potentially eligible studies were obtained. Studies not meeting the inclusion criteria were excluded. In case of doubt, KA was consulted. PM extracted the following data from each pharmacokinetics or safety study: patient population and study design characteristics such as population, number of patients, age, weight, condition (drugs, medical disorders), paracetamol drug information (dose, form), number of samples and study duration. For pharmacokinetics studies, ageing-related changes in the pharmacokinetics of paracetamol (and its metabolites) were extracted, such as clearance and volume of distribution with or without comparison with younger subjects. For safety studies, safety markers (i.e. gastrointestinal, hepatic and renal) were extracted with or without comparison with younger subjects.

3 Results

3.1 Study Selection and Data Extraction

A total of 6088 potentially relevant studies were identified, four of which were obtained through reference checking or manual searching. After removal of duplicates, titles and abstracts of 4864 were screened for potential relevancy. Full texts were obtained for 259 studies, of which 232 were excluded. The most important reason for exclusion was simultaneous analyses of results of young and older patients without subpopulation data, or inclusion of only younger subjects. Consequently, 27 studies were included, of which 20 were pharmacokinetics studies and seven were safety studies. Figure 3 outlines the selection flow chart.

Paracetamol pharmacokinetics will be discussed first according to the ADME (absorption, distribution,

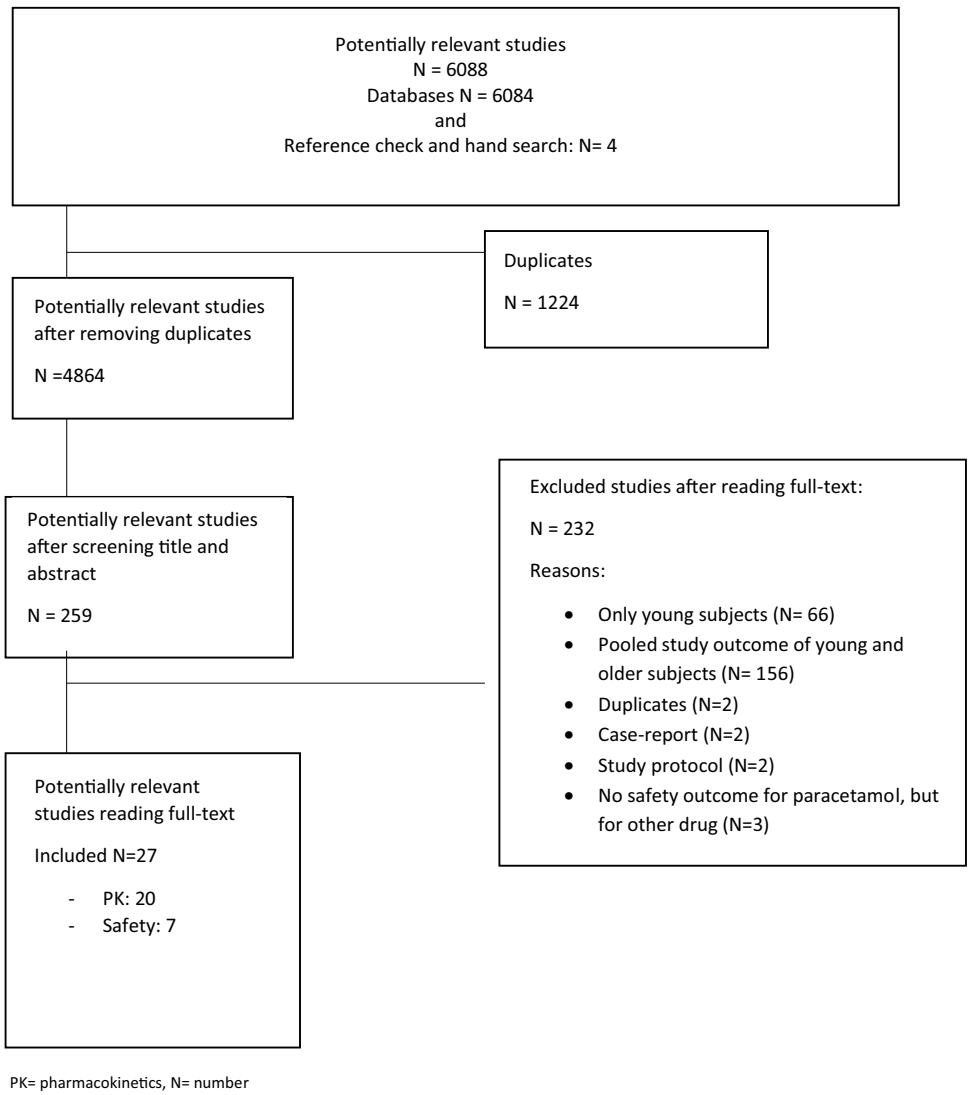

Fig. 3 Flowchart of the screening process

metabolism, elimination) sequence. Thereafter, safety data will be discussed per type of adverse event arising from the search, namely hepato-, nephro- and gastrointestinal toxicity.

3.2 Pharmacokinetics-Related Changes for Paracetamol in Older People

3.2.1 Characteristics of the Pharmacokinetics Studies

Twenty studies on paracetamol pharmacokinetics were included [24–43]. Eighteen reported on pharmacokinetics parameters, the other two focused mainly on the amount of paracetamol metabolites in older people during prolonged administration [34, 35]. Table 2 provides the characteristics of the included pharmacokinetics studies. The numbers of young and older subjects included in the study ranged from 6 to 28 and 7 to 30, respectively. When all studies were combined, the numbers of young and older subjects were 172 and 314, respectively. Mean or median age and weight of the youth varied from 21 to 30 years and 61 to 81 kg and those of the older people from 66 to 89 years and 52 to 88 kg. Conditions for young and healthy older subjects were ambulatory and active. Frail older people were considered to be dependent of continuous care. The pharmacokinetics parameters derived from literature are provided in Fig. 4 and Table S2A–C (see ESM) for the individual studies as retrieved in the search. Using the ADME sequence, the results of these studies are summarised (see Sects. 3.2.2 to 3.2.4).

3.2.2 Influence of Ageing on Paracetamol Absorption

Only three studies compared the oral bioavailability (F) of paracetamol between young and older volunteers based on both oral and intravenous administration in a paired analysis [28, 30, 41] (Table S2). F was similar between young (mean [SD] 98% [0.3]) and older (95% [11]) subjects, as reported by Fulton et al. [41]. Divoll et al., however, reported that older subjects tended to show a reduced F of both tablets (median [range] 72% [57–95]) and elixir (80% [64–94]) compared with younger subjects (79 [59–92] and 87 [70–106], respectively) [29]. However, statistical significance, but not clinical relevance, was attained. In another study from Divoll et al., the influence of age on the potential food–paracetamol interaction was investigated [28]. When paracetamol was administered sober, the F of the elixir (median [range] 80% [64–94]) or tablets (72 [57–95]) tended to be significantly lower in older subjects compared with younger ones (89 [70–106] and 81 [71–92]). When either of them was co-administered with food, there were no differences between the age groups [28].

Three studies investigated the possibility of an association of age with gastric emptying (Table S2, see ESM). They found a similar lag time (t_{lag}) and absorption half-life ($t_{1/2abs}$) between younger and older subjects, namely a t_{lag} (median [interquartile range] of 0.16 h [0.08–0.20] and 0.16 h [0.12–0.22] and a $t_{1/2abs}$ of 0.11 h [0.06–0.18] and 0.12 h [0.07–0.33], respectively) [26]. Divoll et al. and Rashid and Bateman confirmed these findings [27, 29]. Considering the effect of food, the $t_{1/2abs}$ was longer in older subjects taking paracetamol elixir ($p < 0.05$), but not when taking tablets ($p > 0.05$), in comparison with younger subjects. The clinical relevance of these results should be interpreted with caution because of the large inter-individual variability irrespective of age [28].

In conclusion, neither rate nor extent of absorption differs clinically significantly between young and robust older subjects. Absorption was not studied in frail older subjects. Therefore, no conclusions can be drawn for this population.

The time at which the maximum concentration is achieved (t_{max}) and the maximum concentration (C_{max}) are often considered to be absorption-related pharmacokinetics parameters. However, these are secondary parameters and not solely dependent of the absorption phase. To be consistent with literature, the information per individual study on t_{max} and C_{max} is reported in Table S2 below the subheading absorption-related parameters (see ESM).

In conclusion, t_{max} did not change with increased age. For C_{max} differences between young and robust older subjects are less consistent. However, there tend to be no significant differences between younger and robust older subjects. No information on frail older adults is reported.

3.2.3 Influence of Ageing on Paracetamol Distribution

Nine studies reported on the volume of distribution (V_d) [24, 25, 29–32, 39–41, 44]. Four studies [37, 38, 42, 43] did not report on V_d, but the V_d was calculated based on the reported clearance (CL) and half-life ($t_{½}$). The V_d in younger subjects was between 0.77 and 1.40 L/kg and between 0.74 and 1.08 L/kg in robust older subjects, resulting in a relative lower V_d of 3.9–22.9% in the older subjects (Table S2 [see ESM], Fig. 4a). However, there is no consistency between the studies on the actual statistical or clinical significance in comparison with younger subjects. The decreased V_d can physiologically be explained by the age-related greater portion of total body weight consisting of fat, which may be expected to have a larger influence on lipophilic than on hydrophilic drugs. The relative hydrophilic character of paracetamol, together with its incomplete distribution into body fat, could cause V_d to decrease with age, with a consequent rising of paracetamol plasma concentration in older people.

Age is not the only thing responsible for changes in the V_d of paracetamol, health condition in the older population can

Table 2 Patient population and study design characteristics of included studies. Studies are presented in alphabetical order by author

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Bannwarth et al. [37] 2001	**O**: $N = 12$ (8.33)	**O**: 89 (4) [84–95][a]	**O**: 59 (10) [45–74][a]	**O**: Long-term therapy with medication for cardiovascular disorders, mild depression, insomnia Mild–moderate pain for osteoarthritis of hip/knee or for arthritis of shoulder Lab values (blood cell count, aminotransferase, serum albumin, creatinine) were in reference range No smokers, no enzyme-inducing drugs, unstable or active diseases	Enteral (capsule)	Day 1: 1000 mg q12 h Day 2–6: 1000 mg q8 h Day 7: 1000 mg q24 h With 150 mL water	*Blood:* Total: 108 Per patient: 9 [0–10 h]	7 days	HPLC
Bedjaoui et al. [31] 1984	$N = 26$ **Y**: $N = 12$ (57.14) **O**: $N = 14$ (50)	**Y**: 23.9 (1.1) [21–26][a] **O**: 81.5 (5.9) [68–90][a] $\mathbf{O_M}$: 79.71[c] $\mathbf{O_F}$: 82.67[c] $\mathbf{Y_M}$: 23.82[c] $\mathbf{Y_F}$: 26[c]	**Y**: 62.3 (6.9) **O**: 51.8 (12.6) weight specified per sex and age group NR	**All**: No medication 48 h before paracetamol administration Hepatic and renal lab values within normal range	Enteral (NR)	500 mg Fasted for 8 h before and 4 h after paracetamol administration	*Blood:* Total: 442 Per patient: 17 [0–12 h]	12 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Briant et al. [32] 1976†	*N* = 56 **Y**: *N* = 28 (50) **O**: *N* = 28 (50)	**Y**: 28.15[c] **O**: 77.95[c] $\mathbf{O_M}$: 77.4[c] $\mathbf{O_F}$: 76.5[c] $\mathbf{Y_M}$: 28.2[c] $\mathbf{Y_F}$: 28.1[c]	**Y**: 66.4[c] **O**: 62.65[c] $\mathbf{O_M}$: 68.8[c] $\mathbf{O_F}$: 56.5[c] $\mathbf{Y_M}$: 74.2[c] $\mathbf{Y_F}$: 58.6[c]	**Y**: No drugs 2 weeks before study, except oral contraceptive, no impaired liver function 3/28: Elevated blood urea level **O**: No drugs 2 weeks before study. No impaired hepatic function, serum albumin levels, haemoglobin levels 17/28: Elevated blood urea level	Enteral (powder)	1000 mg Fasted overnight With little water	*Blood:* Total: 280 Per patient: 5 [0–6 h]	6 h	Gas–liquid chromatography
Divoll et al. [30] 1982†	*N* = 32 **Y**: *N* = 16 (50) **O**: *N* = 16 (50)	**Y**: 29.05 [23–37][b] **O**: 69.7 [61–78][b] $\mathbf{Y_M}$: 30.8 [24–37][b] $\mathbf{Y_F}$: 27.3 [23–33][b] $\mathbf{O_M}$: 70.3 [61–77][b] $\mathbf{O_F}$: 69.1 [64–78][b]	**Y**: 61.2 [47.7–72.7][b] **O**: 69.6 [45.5–90.9][b] $\mathbf{Y_M}$: 68.2 [59.1–72.7][b] $\mathbf{Y_F}$: 54.2 [47.7–65.9][b] $\mathbf{O_M}$: 79.1 [64.5–90.9][b] $\mathbf{O_F}$: 60.1 [45.5–81.8][b]	**Y**: No diseases, no co-medication **O**: Ambulatory, active, good general health 3/16: Medication for cardiovascular diseases	IV	650 mg	*Blood:* Total: 480 Per patient: 15 [0–12 h]	12 h	HPLC
Divoll et al. [29] 1982	*N* = 28 **Y**: *N* = 16 (50) **O**: *N* = 12 (50)	**Y**: 28.4 [22–39][b] **O**: 70.7 [61–78][b]	**Y**: 64.5 [47.7–86.4][b] **O**: 70.4 [45.5–90.9][b]	**Y**: No diseases, no co-medication **O**: Ambulatory, active, good general health 3/16: Medication for cardiovascular diseases	Enteral (tablet and elixir) and IV	650 mg 1 week elapsing between administration routes Enteral: fasted overnight and 3 h after intake	*Blood:* Total: 448 Per patient: 16 [0–12 h]	12 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Divoll et al. [28] 1982	*N* = 24 **Y**: 12 (50) **O**: 12 (50)	NR	NR	**Y**: Free of any identifiable medical disease **O**: Ambulatory, active, good, general health 3/12: Use of cardiovascular drugs	Enteral (elixir or tablet) or IV	650 mg Administered on 5 occasions separated by 1 week 1. IV 2. Tablets with 100–200 mL water 3. Elixir with 19.5 mL water 4. Tablets 30 min after standardised breakfast 5. Elixir 30 min after standardised breakfast 2 + 3: Fasted overnight and fasted 3 h after intake 4 + 5: Fasted 3 h after intake	*Blood:* Total: 384 Per patient: 16 [0–12 h]	12 h	HPLC
Ellmers et al. [42] 1990	*N* = 55 $\mathbf{O}_{\mathbf{fit}}$: 29 (37.9) $\mathbf{O}_{\mathbf{frail}}$: 26 (42.3)	$\mathbf{O}_{\mathbf{fit}}$: 77.3 (8.2) [64–94][a] $\mathbf{O}_{\mathbf{frail}}$: 83.5 (7.3) [64–97][a]	NR	$\mathbf{O}_{\mathbf{fit}}$: Living independently $\mathbf{O}_{\mathbf{frail}}$: Not living independently, mobility score from 1 to 5	Enteral (tablet)	1000 mg	*Blood:* Total: 330 Per patient: 6 [0–24 h] *Urine:* [0–24 h]	24 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Fulton et al. [41] 1979	*N* = 23 **Y:** *N* = 11 (NR) **O:** *N* = 12 (NR)	**Y:** 23.9 (1.2)[d] **O:** 75.8 (1.6)[d]	NR	**All**: No drugs inducing hepatic microsomal oxidation Normal values of serum bilirubin, aspartate transaminase, alkaline phosphatase, albumin and renal function (sodium, potassium, bicarbonate, urea, creatinine)	Enteral (tablet) and IV	500 mg Separated occasions 1 wk apart	NR	6 h	Gas chromatography
Gainsborough et al. [26] 1993	*N* = 38 **Y**: 19 (NR) **O**: 19 (NR)	**Y**: 24.8 [20–33][b] **O**: 75.0 [69–86][b]	NR	**All**: No gastric, oesophageal, liver or other diseases No drugs, alcohol, cigarettes 24 h before paracetamol intake	Enteral (tablet)	20 mg/kg with 250 mL water Fasted 9 h before intake	*Blood:* Total: 570 Per patient: 15 [0–3 h]	3 h	Enzyme-specific method

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Hagen et al. [36] 1991	*N* = 22 **Y**: 6 (50) **O**: 16 (18.75)	**Y**: 30 [NR][b] **O**: 81 [70–90][b]	**Y**: 67 [55–80][b] **O**: 54 [35–72][b]	**All**: No ongoing paracetamol treatment, dementia/ confusion, malabsorption disorders, inflammatory or malignant intestinal disease, decompensated heart failure, liver disease, kidney insufficiency or hyper- or hypofunctioning of thyroid **Y**: Healthy **O**: Stable clinical condition, aged > 70 years 9/16: Faeces in rectum	Enteral (suppository)	500 mg Fasted overnight and for 2.5 h after intake	*Blood:* Total: 154 Per patient: 7 [0–8 h]	8 h	NR
Kamali et al. [43] 1993	*N* = 19 O_H: 9 (78) O_{NIDDM}: 10 (90)	O_H: 69.3 (2.3) O_{NIDDM}: 67.1 (3.0)	O_H: 70.5 (10.9) O_{NIDDM}: 77.0 (9.6)	**All:** Normal renal and hepatic function, no smokers O_{NIDDM}: Received combination of hypoglycaemic agents and restricted carbohydrate intake. 7/10 patients received other cardiovascular drugs (not taken during the study period)	IV	500 mg	*Blood:* Total: 228 Per patient: 12 [0–6 h] *Urine:* Before study [0–24 h]	24 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Liukas et al. [39] 2011	$N=40$ $\mathbf{Y}_{\mathbf{20\text{-}40y}}$: $N=10$ (70) $\mathbf{O}_{\mathbf{60\text{-}70y}}$: $N=10$ (50) $\mathbf{O}_{\mathbf{70\text{-}80y}}$: $N=10$ (60) $\mathbf{O}_{\mathbf{80\text{-}90y}}$: $N=10$ (10)	$\mathbf{Y}_{\mathbf{20\text{-}40y}}$: 27 (5) $\mathbf{O}_{\mathbf{60\text{-}70y}}$: 66 (3) $\mathbf{O}_{\mathbf{70\text{-}80y}}$: 77 (3) $\mathbf{O}_{\mathbf{80\text{-}90y}}$: 84 (3)	$\mathbf{Y}_{\mathbf{20\text{-}40y}}$: 81 (14) $\mathbf{O}_{\mathbf{60\text{-}70y}}$: 83 (9) $\mathbf{O}_{\mathbf{70\text{-}80y}}$: 82 (13) $\mathbf{O}_{\mathbf{80\text{-}90y}}$: 68 (8)	**All**: No hepatic, renal, neurological, endocrine, haematological, metabolic or gastrointestinal diseases, BMI > 35 kg/m^2, strong inhibitors or inducers of cytochrome P450 enzymes **Y**: Arthroscopic anterior crucial ligament operation of knee **O**: Elective knee prosthesis operation	IV	1000 mg	*Blood:* Total: 880 Per patient: 22 [0–24 h]	24 h	HPLC
Miners et al. [38] 1988	$N=16$ **Y**: $N=8$ (100) **O**: $N=8$ (100)	**Y**: 20.8 (2.4) [18–26][a] **O**: 79.3 (7.2) [72–92][a]	**Y**: 74.9 (5.3) [69–82][a] **O**: 77.2 (3.0) [72–87][a]	**Y**: Healthy, no medication 1 week before study, non-smokers **O**: Ambulatory, no drug influencing paracetamol metabolism or extensively conjugated, non-smokers, no respiratory, unstable cardiac, renal, hepatic diseases Liver and renal lab values within reference range	Enteral (tablet)	1000 mg Fasted overnight and 3 h after intake	*Blood:* Total: 160 Per patient: 10 [0–8 h] *Urine:* [0–12 h]	12 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Moreau et al. [40] 1993	**O**: $N=12$ (75)	**O**: 77 (7) $\mathbf{O_M}$: 77.78 (NR) $\mathbf{O_F}$: 75 (NR)	**O**:66 (15) $\mathbf{O_M}$:70.55 (NR) $\mathbf{O_F}$:53 (NR)	**O**: Operation due to arthritis of the lower limbs (continuous spinal anaesthesia) Exclusion: No paracetamol 48 h before study Insufficient liver or renal function, paracetamol allergy	IV	2000 mg propacetamol chloral hydrate (= 1000 mg paracetamol)	*Blood and CSF:* Total: 168 Per patient: 14 [0.25–6 h]	6 h	HPLC
Pickering et al. [35] 2011	$N=30$*	65 (11)	77 (14)	**All**: Aortic surgery patients No clearance rate < 30 mL/min	IV	1000 mg q6 h	*Blood:* Total: 60 Per patient: 2 [days 0 and 4] *Urine:* [0–24 h] on days 0 and 4	4 days	HPLC
Pujos-Guillot et al. [34] 2012	**O**: $N=10$	74.0 (1.2)[d]	74.2 (3.6)[d]	**O**: Arthritic pain No treatment with N-acetylcysteine	NR	3000 mg/day	*Blood:* Total: 20 Per patient: 2 [days 0 and 14] *Urine:* [0–24 h] days 0 and 14	14 days	HPLC
Rashid and Bateman [27] 1990**	$N=14$ **O**: 7 **Y**: 7	**O**: 70 (1.6)[e] **Y**: 23 (1.3)[e]	NR	No history of gastrointestinal or renal disease, no concurrent medication, no paracetamol in wash-out weeks, no alcohol, drugs or smoking for 48 h before study Normal physical examination and ECG	Enteral (solution)	1000 mg 10 min after intake placebo or atropine Fasted overnight and 2 h after paracetamol intake	*Blood:* Total: 168 Per patient: 12 [0–6 h]	6 h	HPLC

Table 2 (continued)

Study	Patient population (male)	Age (years)	Weight (kg)	Conditions	Route of administration	Dose and other administration specifications	Sampling [sampling period]	Study duration	Analytical method
Robertson et al. [33] 1992***	**O**: $N=8$	**O**: 73 [65–78][b]	**O**: 78.8 [71–90][b]	**O**: Healthy, no history of gastrointestinal disease. One subject received medication (digoxin, warfarin). These were not taken on the morning of the study. One subject smoked (no smoking 2 weeks before study)	Enteral (solution)	1500 mg with 100 mL water Overnight fast and semi-recumbent for 4 h after dose	*Blood:* Total: 144 Per patient: 18	4 h	NR
Triggs et al. [25] 1974	$N=13$ **Y**: $N=6$ (100) **O**: $N=7$ (100)	**Y**: 24 [22–30][b] **O**: 80.9 [73–91][b]	**Y**: 75.17 [60–95][b] **O**: 57.14 [51–68][b]	**All**: Serum urea, creatinine, bilirubin, alkaline phosphatase, GOT, GPT, plasma protein in normal range **Y**: No medication 48 h before paracetamol administration **O**: 3/7 other medication (digoxin, methyldopa)	Enteral (oral solution)	14.3 mg/kg 2 h after breakfast	*Blood:* Total: 132 Per patient: 8 (Y), 12 (E) [0–7 h]	24 h	NR

Data are presented as median [range] or mean (SD) unless otherwise specified: [a]mean (SD) [range], [b]mean [range], [c]mean, [d]mean (SEM)

CSF cerebrospinal fluid, *ECG* electrocardiogram, *GOT* glutamate oxaloacetate transaminase, *GPT* glutamic pyruvic transaminase, *HPLC* high-performance liquid chromatography, *IV* intravenous, *NR* not reported, *O* older people, O_F older female, O_H healthy older people, O_M older male, O_{NIDDM} older patient with non-insulin-dependent diabetic mellitus, *q* (quaque) every, *SEM* standard error of the mean, *Y* young subject, Y_F young female, Y_M young male, *y* years

*As influence of age was a secondary aim of this study, the study did not specify the number of subjects in young and older subgroups for number of patients, weight and age

/*This paper compared paracetamol vs paracetamol + atropine (**) or paracetamol vs paracetamol + levodopa (***), where paracetamol served as a marker for gastric emptying. Only the paracetamol pharmacokinetic values without influence of atropine/levodopa are presented

[†]Characteristics of patients in this study were specified separately for men and women and are expressed as the mean of these two groups together in this table

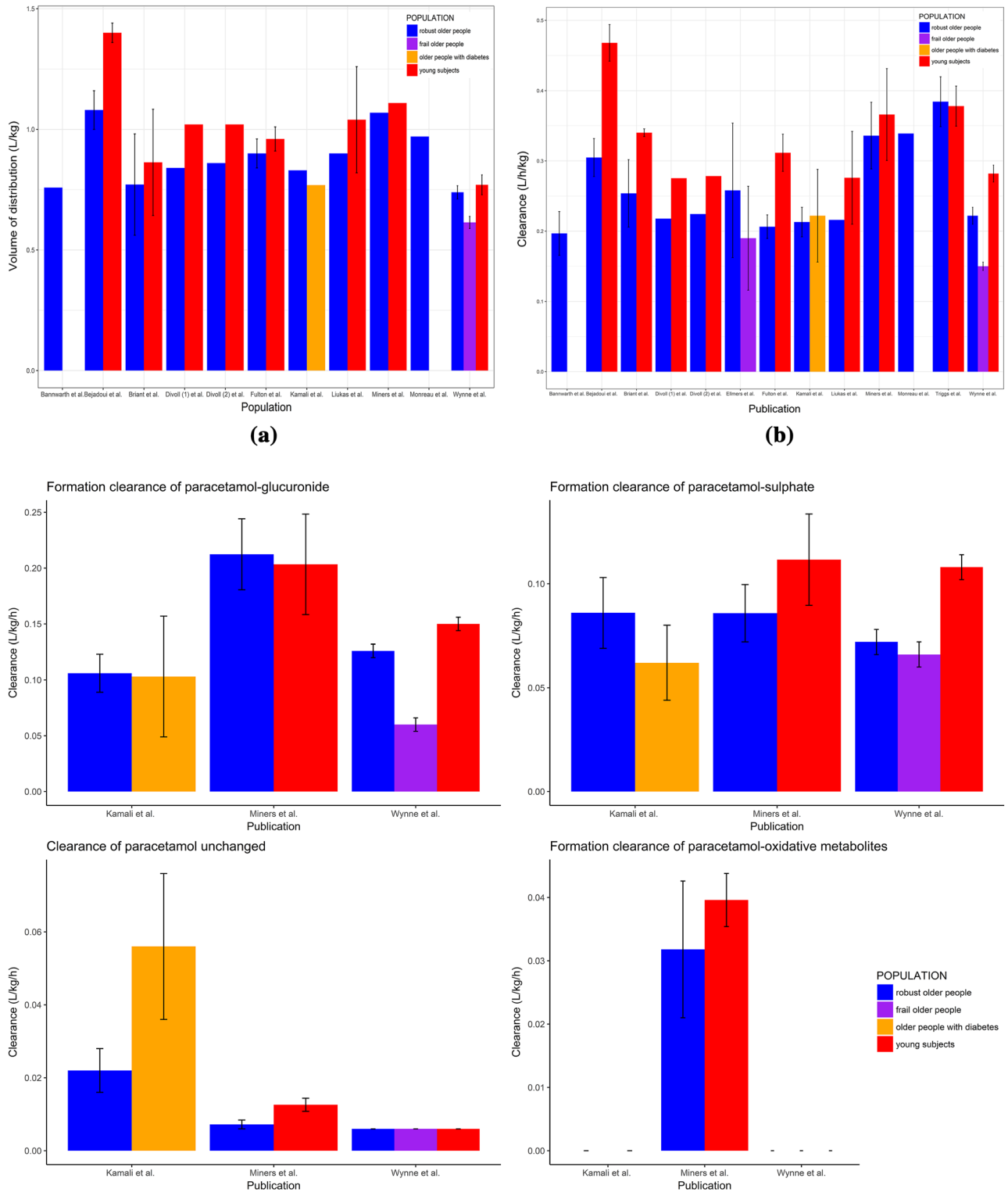

Fig. 4 **a** Volume of distribution (L/kg), **b** clearance (L/kg/h) values of paracetamol and **c** formation clearance (L/kg/h) values from paracetamol to its metabolites (in young and older subjects derived from literature). Notes: For Liukas et al. [39], the clearance values of the older subgroups used in their original study (60–70, 70–80, 80–90 years) were pooled to obtain one 'older people' clearance value. For Bannwarth et al. [37], Kamali et al. [43] and Miners et al. [38], the volume of distribution was not reported but calculated based on the reported clearance and half-life by study

also affect pharmacokinetics. Wynne et al. studied the association of age and frailty on the V_d (L/kg) of paracetamol. They reported the lowest V_d in frail older people, namely 16.9 and 20.3% lower (not statistically significant) in comparison with robust older and young subjects, respectively [24]. Ellmers et al. support this finding, be it with only a decrease (4.7%) in frail compared with robust older people [42], possibly due to small subgroups and a large degree of variability within the subgroups. Comparing robust older subjects with those with diabetes mellitus, only a small decrease (7%) in V_d was noted in older subjects with diabetes [43].

Five studies [30–32, 40] investigated sex-related differences in pharmacokinetic parameters between robust male and female older adults, of which four studies reported a smaller V_d in women compared with men ($p < 0.05$), ranging from 8.5 to 17.5% [30–32]. This is probably caused by the larger proportion of fat in a woman's total body weight.

It is reasonable to state that V_d decreases with increasing age, most pronouncedly in frail older people. Changes in V_d determine the influence of the loading dose, and the elimination half-life. Both statistical and clinical significance are still unknown.

3.2.4 Influence of Ageing on Paracetamol Metabolism and Elimination

Eleven out of 13 studies reported reduced paracetamol CL (29–45.7%), varying from 0.20 to 0.38 L/h/kg in robust older subjects and 0.28 to 0.7 L/h/kg in younger subjects (Fig. 4b, Table S2 [see ESM]), while Miners et al. [38] and Triggs et al. [25] reported no significant differences. Another study, comparing paracetamol CL on days 1 and 7 during repeated administration, reported no paracetamol accumulation. However, this does not imply anything regarding possible accumulation of the (toxic) metabolites.

Additional factors besides age, such as disease, concomitant medication or general physical status (e.g. frailty), may influence paracetamol metabolism. Ellmers et al. reported a significant decrease (26.4%) in paracetamol CL in frail compared with robust older subjects [42], which was supported by Wynne et al. when paracetamol CL was expressed in terms of body weight [24]. Paracetamol CL was 46.8% lower in frail older subjects compared with young subjects ($p < 0.01$) and 32.4% lower compared with robust older subjects ($p < 0.01$). When CL was expressed per unit volume of liver, no significant differences were found between young and robust older subjects, but it was significantly reduced in the frail subjects: 37.5 and 32.9% lower when compared with young and robust older cases, respectively. This indicates that frailty and/or disease state also decreases CL. No difference (4%) in paracetamol CL was reported between older subjects with and without diabetes [43].

A few pharmacokinetics studies focused on the contribution of the different metabolic routes (Fig. 4c), with conflicting results. Miners et al. reported no significant change in the formation fraction to glucuronide and to oxidative metabolites [38]. However, formation fraction to sulphate and the excretion of unchanged paracetamol was 18.2 and 30.0% lower in older subjects compared with their younger counterparts [38]. Pickering et al. reported a significant decrease in the amount of sulphate excreted in urine in participants aged ≥ 65 years but not in those < 65 years, with a decrease in glutathione reserves and some more oxidative metabolites ($p > 0.05$) [35]. Next to a significant 36.4% decrease in fraction of sulphate (in robust older vs young subjects), another study reported also a significant 13.3% decrease in formation fraction of glucuronide (in robust older vs young subjects), but reported no differences in excretion of unchanged paracetamol between young and robust older subjects [24]. The oxidative metabolites were not measured. However, when calculating the fraction based on the fact that this is the remaining unexplained part of the total paracetamol CL, there seems to be no difference between young and robust older subjects. For frail older subjects, the formation fractions of glucuronide and sulphate were decreased compared with the young (60 and 40%, respectively) and robust older subjects (53.9 and 5.7%, respectively) [24]. For older people with diabetes, a significant decrease in formation fraction to sulphate (33.3%) and a significant increase in renal excretion of unchanged paracetamol (50%) compared with robust older subjects were reported. The formation fraction of glucuronide remained unchanged.

In conclusion, paracetamol CL decreases not only with age but even more with frailty and/or disease state. Conflicting and limited results about the fractions of paracetamol into the different metabolic pathways still exist.

A secondary pharmacokinetics parameter, $t_{½}$, is directly related to V_d and inversely to CL. This parameter will not be discussed in the text but is reported in Table S2 (see ESM) for the individual studies.

3.3 Safety-Related Changes for Paracetamol in Older People

Seven studies reported on adverse events (hepatotoxicity, nephrotoxicity and gastrointestinal toxicity) [45–51], possibly related to paracetamol use in older subjects. The studies are presented in detail in Table 3 while patterns of safety-related changes in older people are summarised below.

Paracetamol hepatotoxicity has been investigated in multiple studies, but with only a few studies focusing on age. Mitchell et al. reported that alanine aminotransferase (ALAT) concentrations in the frail older and robust older subjects were within and slightly above the reference range, respectively, while the highest serum ALAT

Table 3 Observations on the safety of paracetamol at therapeutic dosages

Adverse event	Study	Study design	Population	Determinant	Paracetamol use	Conclusions
Hepatotoxicity	Mitchell et al. [45]	Observational cohort study	*Young* Paracetamol group: $N=11$ [mean age (SD): 35.6 (11.9)] Control group: $N=8$ [46.3 (13.2)] *Fit older* Paracetamol group: $N=12$ [81.7 (5.4)] Control group: $N=12$ [81.0 (5.5)] *Frail older* Paracetamol group: $N=13$ [85.4 (6.2)] Control group: $N=15$ [83.1 (4.7)]	ALAT at baseline, on day 5 Paracetamol concentration on day 5	Oral paracetamol group: 3000–4000 mg per day Control group: NR	ALAT in older robust and frail subjects within and slightly above reference range Highest serum ALAT in young subjects Older frail subjects receiving lowest paracetamol dosage had highest paracetamol concentration on day 5
Hepatotoxicity	Jahr et al. [46]	Pooled analysis of 3 randomised placebo-controlled trials	*Young* (< 65 y) Paracetamol group: $N=56$ [50.45 years] Control group: $N=68$ [31.5] *Older* Paracetamol group: $N=48$ [73.8] Control group: $N=49$ [71.9]		Intravenous paracetamol group: 1000 mg Control group: NR	**Study 1**[a] Normal: $p=0.481$ > 1 ULN to < 3 ULN: $p=0.585$ ≥3 ULN: $p=1.000$ **Study 2** Normal: $p=0.438$ > 1 ULN to < 3 ULN: $p=0.634$ ≥3 ULN: $p=1.000$ **Study 3** Normal: $p=0.449$ > 1 ULN to < 3 ULN: $p=1.000$ ≥3 ULN: $p=1.000$ No significant difference between paracetamol and placebo groups in older subjects concerning liver function values Overall incidence of adverse events was comparable between paracetamol and placebo groups and between age groups

Table 3 (continued)

Adverse event	Study	Study design	Population	Determinant	Paracetamol use	Conclusions
Nephrotoxicity	Koppert et al. [48]	Randomised placebo-controlled study	*Older:* $N=75$ (mean [range] 76.5 y [65–94]; 70.9 kg [47–127]	Markers of renal function (serum Cystanin C, creatinine, blood urea nitrogen, creatinine clearance, urinary sodium, potassium, albumin, alfa-1-microglobulin)	Intravenous paracetamol: 1000 mg Parecoxib: 40 mg Saline: NR	Decrease in creatinine clearance in the paracetamol group (−17.1 mL/min) and placebo group (−23.4 mL/min) ($p>0.05$) First 2 h after initial dose of parecoxib, creatinine clearance decreased (−49.2 mL/min) ($p<0.05$) All treatment groups: urine albumin, alfa-1-microglobulin, sodium and potassium were slightly increased ($p>0.05$)
Gastrointestinal toxicity	Alexander et al. [47]	Hospital prescribing case–control study	*Older* In-patients: $N=1878$ Control: NR	Diagnosis of gastrointestinal bleeding and paracetamol use	Any paracetamol dose	No differences in paracetamol use between inpatients and control with gastrointestinal bleeding
Gastrointestinal toxicity	Langman et al. [49]	Case–control study	*Older* Patients: $N=1121$ Control: $N=2115$	Diagnosis of gastrointestinal bleeding and paracetamol use	Any paracetamol dose	Paracetamol use was not associated with either gastric or duodenal ulcer bleeding
Gastrointestinal toxicity	Rahme et al. [51]	Population-based retrospective cohort study	*Older* $N=21,207$ (with paracetamol prescription) (26,978 with NSAID prescription)	High or low paracetamol (or NSAID) prescription and rates of gastrointestinal events	High-dose paracetamol: 2601–3250 or > 3250 mg/day Low-dose paracetamol: < 2600 mg/day	RR high-dose paracetamol: 1.27 [95% CI 1.13–14.3] RR low-dose paracetamol: 1.34 [95% CI 1.15–1.54] RR high-dose NSAID: 0.98 [95% CI 0.85–1.13]
Gastrointestinal toxicity	Rahme et al. [52]	Population-based retrospective cohort study	*Older* $N=644,183$ High-dose paracetamol: 1,597,725 (31.6% with PPI) prescriptions Low-dose paracetamol: 3,641,140 (28.3% with PPI) prescriptions	High- or low-dose paracetamol with or without PPI (combination of NSAID and paracetamol with or without PPI or NSAID with or without PPI)	High-dose paracetamol: > 3 g/day Low-dose paracetamol: ≤ 3 g	In comparison with low-dose paracetamol without PPI: HR high-dose paracetamol without PPI: 1.2 [1.03–1.40] HR high-dose paracetamol with PPI: 0.95 [0.81–1.11] HR NSAID and paracetamol without PPI: 2.15 [1.35–3.40] HR NSAID and paracetamol with PPI: 2.55 [1.98–3.28]

ALAT alanine amino-transferase, *CI* confidence interval, *HR* hazard ratio, *N* number of patients, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drugs, *PPI* proton pump inhibitor, *RR* relative risk, *ULN* upper limit of normal

[a]Values only reported for older subjects

concentrations were observed in the younger subjects [45]. Although frail older adults received the lowest dosages of paracetamol, paracetamol concentrations were highest in this group [45] (Table 3). In patients > 65 years of age, Jahr et al. found no significant differences in liver enzyme values between the paracetamol and placebo groups (Table 3) [46]. The overall incidence of adverse events was comparable between the paracetamol and placebo groups and between the young and older subjects. A detailed overview of all the adverse events specified in the three individual studies can be found in the paper of Jahr et al. [46].

One study investigated the effect of paracetamol, parecoxib and placebo on the renal function in older people [48] (Table 3). No significant decrease in creatinine CL was observed in both the paracetamol group and placebo group. For all treatment groups, urine albumin, α-1-microglobulin, sodium and potassium were slightly, but not significantly, increased.

Four retrospective studies [47, 49, 51, 52] explored the association between paracetamol use and gastrointestinal toxicity, of which two studies reported no significant differences in paracetamol use between hospitalised patients and controls with gastrointestinal bleeding [47, 49] or duodenal ulcer bleeding [49]. Rahme et al. concluded that (after adjustment for 'risk susceptibility'—likelihood of receiving paracetamol e.g. older, sicker, with prior gastrointestinal events) patients who took higher-dose paracetamol (2601–3250 or > 3250 mg/day) were more likely to experience a gastrointestinal event compared with those who took low-dose paracetamol (≤ 2600 mg/day) [51]. These higher-dose paracetamol users experienced similar rates of gastrointestinal events as patients who took a high-dose non-steroidal anti-inflammatory drug (NSAID) [51]. Another study by Rahme et al. reported an increased (non-significant) risk of gastrointestinal events in the high- versus low-dose paracetamol group without a proton pump inhibitor (PPI); this risk was slightly less when the low-dose group used a PPI. The highest risk was in the combination group of NSAID and paracetamol with or without a PPI (Table 3) [52].

In conclusion, a very limited number of studies concluded that paracetamol administration at therapeutic doses (3000–4000 mg/day) did not result in elevated liver enzymes in older people and that glomerular and tubular functions were transiently affected in all older people after orthopaedic surgery. However, the effects were limited and not significant. The evidence concerning the increased risk of gastrointestinal events after paracetamol usage remains inconsistent and therefore not convincing. Overall, due to limited and heterogeneous evidence, it was difficult to drawn firm and meaningful conclusions on changed risk in paracetamol safety in older people.

4 Discussion

In this review, we applied the paediatric study decision tree [21, 22] extrapolated to robust and frail older people for paracetamol. Based on this study decision tree concept, we performed a search on what is already known on pharmacokinetics and safety to delineate the knowledge gaps. Our ultimate goal is to describe a roadmap to reach evidence-based dosing advice for this heterogeneous and increasing population. Concerning the pharmacokinetics studies of paracetamol in older subjects, many ($n = 20$) non-compartmental pharmacokinetics analyses were performed (Table 2 and Table S1 [see ESM]), most of which compared paracetamol pharmacokinetics between young and (robust) older subjects. The limited number of studies ($n = 3$) included in this review revealed no changes in absorption with ageing [28, 29, 41]. In contrast, the V_d was decreased in older subjects and even further decreased in frail older subjects compared with younger subjects. (Table S2 [see ESM], Fig. 4a). Similar to V_d, age and frailty are associated with reduced paracetamol CL (Table S2 [see ESM], Fig. 4b). This review reveals that pharmacokinetics-related knowledge gaps still remain, and these will be discussed below. Thereafter, we will focus on what is already known on safety and subsequently highlight the safety-related knowledge gaps.

Although this review showed cumulative evidence around the impact of age and frailty on pharmacokinetics parameters, re-illustration of the importance of other factors in this special population of older adults, such as drug- and patient-specific factors (e.g. potential covariates) that could influence paracetamol pharmacokinetics are underreported or unknown. For drug-specific factors, limited research, especially on absorption, has been conducted on paracetamol when rectally administered in robust and frail older subjects. In addition, new routes of administration (buccal) are investigated, which should also be investigated in relation to the pharmacokinetics of oral and/or intravenous routes [53, 54]. Concerning the patient-specific factors, the older patient population is very heterogeneous (e.g. robust, frail, polypharmacy comorbidities). When focusing on robust older subjects, the focus of the performed pharmacokinetics studies is mainly on the question of whether a significant difference in pharmacokinetics parameters exists between the above-mentioned group and young subjects. This is certainly important when performing a first pharmacokinetics study. However, this review revealed differences in pharmacokinetics parameters such as V_d and CL between young and older robust subjects. Consequently, the question should no longer be if the difference is statistically significant, but whether the difference in CL and/or V_d in robust older

subjects is clinically relevant enough for dose adaptation in older people.

Population pharmacokinetics modelling can be a useful tool, not only to predict pharmacokinetics parameters, but also to develop more evidence-based dosing in special populations [55]. Patient-related (i.e. age, frailty, multi-morbidity, polypharmacy) and treatment characteristics (i.e. route of administration) can thereby be used to (partly) understand and explain the inter-individual and intra-individual variability in these pharmacokinetics parameters in older subjects. Therefore, those covariates can be used to determine if and how dosing can be individualised. After the development of such a pharmacokinetics model, the dosage needed to reach a specific target concentration can be developed. The target concentration (C_{ssmean}) to reach analgesia is 10 mg/L [56]. This specific value as a target concentration in older subjects is not specifically investigated, but can be assumed to be similar. After the development of a pharmacokinetics model and model-based dosing, it would be of the utmost importance to prospectively validate the model-based dosing in a clinical study, not only to investigate whether the target concentration is reached, but also to investigate if the safety values are within the reference range. A first step could be to evaluate the already performed pharmacokinetics studies on quality and the amount of data, such as clinical characteristics, drug concentrations in plasma, number of patients and time of sampling, retrieved from these studies in order to perform a pooled-pharmacokinetics analysis [55]. Such a pooled analysis has already been performed by Allegaert et al. [57] with the aim to study all common covariates in adults in datasets on intravenous paracetamol. In this way, a pooled analysis could be performed with all pharmacokinetics data of the older population. After developing a pharmacokinetics model specific for older people, a next step could be to design a new study with specific focus on, for example, additional covariates that have not yet been studied in already published datasets and that could possibly explain the residual variability. In this way, we should use these already available datasets and published Pop pharmacokinetics models to put new datasets into these perspectives. This is a very effective approach to explore additional covariates or specific subpopulations, but should be preceded by a critical assessment of the published models [39, 58].

After this information has been collected for the more homogenous population within the older population, studies can be extended to investigate the influence of frailty on the pharmacokinetics of paracetamol. Until now, only two studies have investigated the difference in paracetamol pharmacokinetics in robust versus frail subjects; clear differences were found between these two older populations [24, 42]. However, a major limitation of these studies is the small number of study participants. Besides, the definition of frailty has since changed, as described in the recent EMA reflection paper on physical frailty [59]. Ellmers et al. defined frailty as immobility (scale 1–5) and living dependently, while Wynne et al. defined frail patients as continuously needing hospital care due to chronic disabling conditions (cerebrovascular or musculoskeletal disease). Despite the limited definitions of frailty, differences in pharmacokinetics parameters between fit and frail existed. Likewise, it has not been investigated if and how dosages should be adapted based on the pharmacokinetics in frail older subjects. Lastly, the influence of common multi-morbidity and polypharmacy in older people on the pharmacokinetics of paracetamol has not yet been investigated.

Another knowledge gap that needs to be further explored is the extent of accumulation of paracetamol and its metabolites, especially the active toxic metabolite of paracetamol, NAPQI (Fig. 1). Bannwarth et al. found no accumulation of paracetamol after 7 days of therapeutic paracetamol dosing [37]. However, future studies should not only focus on paracetamol, but also on the toxic metabolite. Data on the fraction of formation of paracetamol into its metabolites are still limited and conflicting (Fig. 4c) and should therefore be investigated. Based on the limited studies focusing on the formation CL of the different metabolites, it seems that age-related changes mostly relate to reduced conjugation capacity, rather than to the formation of the oxidative metabolite. This review shows that most studies used high-performance liquid chromatography analysis to measure paracetamol as well as its metabolites. By using this method it is difficult to quantify oxidative metabolites due to assay sensitivity issues [13]. As ultra-performance liquid chromatography–mass spectrometry techniques are available (and validated) to measure paracetamol and all metabolites, these can be used in future studies [13].

Compared with the large number of pharmacokinetics studies performed, very few studies addressed the safety of paracetamol when administered at regular doses. One of the main concerns, in any population, is the risk of hepatotoxicity [17]. A source of information concerning age-related changes to toxicological mechanisms in paracetamol is reported by Mitchell et al. [60]. Raised values of liver enzymes have been reported even when paracetamol was administered at normal dosages in healthy adults [61]. Based on the—albeit limited—observations retrieved in our search, there is no evidence that supports a higher incidence of hepatotoxicity in normal paracetamol dosages in older subjects [45, 46]. This is in line with the fact that age-related changes in paracetamol formation CL mostly occur in impaired conjugation rather than in the formation of oxidative metabolites [24, 35, 38]. Overall, due to limited and heterogeneous evidence, it was difficult to draw firm and meaningful conclusions on changed risk in paracetamol safety in older people. Safety of paracetamol (i.e. hepatic, gastrointestinal) should be investigated more profoundly,

preferably simultaneously with pharmacokinetics, in clinical trials but also in the clinical setting.

5 Conclusion

Differences in paracetamol CL and V_d between young and robust older people have been reported, with an even further decrease in those pharmacokinetics parameters in frail older people. Based on the—albeit limited—observations retrieved in our search, there is no evidence that supports a higher incidence of hepatotoxicity in paracetamol at normal dosages in older subjects. Overall, due to limited and heterogeneous evidence, it was difficult to drawn firm and meaningful conclusions on changed risk for paracetamol safety in older people. Population pharmacokinetics modelling can be considered a valuable tool to develop more evidence-based dosing advice for older people. In addition, more clinical studies with enriched clinical characteristics (e.g. comorbidity, comedication, frailty) should be conducted to study both the pharmacokinetics of paracetamol (and its metabolites) and its safety parameters.

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Compliance with Ethical Standards

Conflict of interest Paola Mian, Karel Allegaert, Isabel Spriet, Dick Tibboel and Mirko Petrovic declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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