1   **A Review of Population Pharmacokinetic Studies of Levetiracetam**

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26 **Abstract**

27 *Background:* Levetiracetam has been widely used as a treatment option for different types of

28 epilepsy in both adults and children. Because of its large between-subject variability, several

29 population pharmacokinetic studies have been performed to identify its pharmacokinetic

30 covariates, and thus facilitate individualised therapy.

31 *Objective:* The aim of this review was to provide a synopsis for population pharmacokinetic

32 studies of levetiracetam and explore the identified influencing covariates.

33 *Methods:* We systematically searched the PubMed and Embase databases from inception to

34 30 June, 2020. The information on study designs, target population, model characteristics, and

35 identified covariates was summarised. Moreover, the pharmacokinetic profiles were compared

36 among neonates, children, and adults.

37 *Results:* Fourteen studies were included, among which 2 involved neonates, 4 involved

38 children, 2 involved both children and adults, and 6 involved only adults. The median value of

39 apparent clearance for children (0.074 [range: 0.038–0.079] L/h/kg) was higher than that for

40 adults (0.054 [range: 0.039–0.061] L/h/kg). Body weight was found to significantly influence

41 the apparent clearance and volume of distribution significantly, whereas renal function

42 influenced the clearance. Likewise, co-administration with enzyme-inducing antiepileptic

43 drugs (such as carbamazepine and phenytoin) increased the drug clearance by 9%–22%,

44 whereas co-administration with valproate acid decreased it by 18.8%.

45 *Conclusion:* Levetiracetam dose regimen is dependent on the body size and renal function

46 of patients. Further studies are needed to evaluate levetiracetam pharmacokinetics in neonates

47 and pregnant women.

48 **Keywords:** levetiracetam; review; population pharmacokinetic; nonlinear mixed effect

49 modelling

50 **Key points**

51 • This review identifies weight, renal function, daily dose, and postmenstrual age as the

52 covariates that most likely influence the levetiracetam (LEV) pharmacokinetics.

53 • Children showed higher clearance per kilogram body weight than adults, indicating

54 that a higher dosage is required for children per kilogram body weight.

55 • Further PPK studies are needed to evaluate LEV pharmacokinetics in special

56 populations such as pregnant women and neonates.

1. Introduction

Levetiracetam (LEV) is a second-generation antiepileptic drug (AED) approved by the FDA to treat different types of epilepsy in both adults and children. Its mechanism of action is different to other AEDs. Studies have shown that LEV exerts its action on a new target, a synaptic vesicle protein 2A (SV2A), and inhibits neuronal (N)-type high-voltage-activated calcium channels [1, 2]. Because of its relatively safe adverse effect profile, LEV is recommended as a first-line therapy for patients with partial-onset seizures and it has replaced valproic acid (VPA) as the most frequently prescribed first-line antiepileptic drug in children since 2012 [3, 4].

LEV, after oral administration, is rapidly and almost completely absorbed (>95%). It reaches a peak plasma concentration (C_{max}) in approximately 1 to 1.5 h after administration. LEV is not bound to the plasma protein, and its volume of distribution (V) ranges from 0.5 to 0.71 L/kg [5]. The drug is mainly metabolised by enzymatic hydrolysis of the acetamide group (27%), whereas the hepatic cytochrome P450 system plays only a small part (2.5%) [6]. Approximately, 66% of LEV is excreted unchanged by the kidney. Therefore, patients with renal impairment may need dose adjustments [6].

Moreover, LEV exhibits a high variability for children and pregnant women [7, 8]. Previous studies have shown lower LEV concentrations in children than in adults following the same dosage per kilogram bodyweight [7]. Likewise, enhanced LEV clearance has been reported in pregnant women [8]. Usually, in clinical practice, therapeutic drug monitoring (TDM) plays a crucial role in dose individualisation for these special patients [9]. However, the TDM approach has certain limitations, as it can only be implemented after treatment initiation. In such cases, population pharmacokinetic (PPK) analysis, which describes typical pharmacokinetic parameters of the target population and identifies factors that contribute to the variability of

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81   LEV, can help determining the appropriate initial LEV dosage for patients. Furthermore,

82   through Bayesian forecasting, the PPK analysis can be developed as a powerful tool to estimate

83   the individual PK parameters and develop dose individualisation, which is widely used in

84   clinical practice [10, 11].

85   To date, several PPK studies on LEV have been conducted to identify the covariates that may

86   have a significant effect on the pharmacokinetics. However, no study has summarised data

87   concerning the PPK modelling of LEV. Thus, the aim of this review was to present an overview

88   of these published PPK studies, summarise significant covariates affecting the LEV

89   pharmacokinetics, and identify any knowledge gaps that remain to be explored.

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91   **2. Methods**

92   **2.1 Information Sources and Search Strategy**

93   All PPK studies on LEV were systematically searched in the PubMed and Embase databases

94   from inception until 30 June, 2020, as per the Systematic Reviews and Meta-Analyses

95   (PRISMA) [12]. The pertinent PPK studies on LEV were identified using the following search

96   terms: 'levetiracetam', 'keppra', or 'elepsia' and 'population pharmacokinetic',

97   'pharmacokinetic modeling', 'nonlinear mixed effect model', 'NONMEM', 'Pmetrics',

98   'WINNONMIX', 'ADAPT', 'P-PHARM', 'nlmixed', 'NLME', 'USC*PACK', or

99   'MONOLIX'. In addition, the reference lists of the selected articles were also checked to

100 identify any related studies. Two authors independently performed the literature search. A third

101 senior investigator was consulted to resolve any discrepancies.

102 All studies identified from databases and other sources were screened to assess their

103 eligibility. A study was considered eligible for inclusion in this review if it met the following

104 criteria: (1) the study population included healthy volunteers or patients; (2) LEV was used as

105   the study drug, regardless of its formulation; (3) the study was focused on PPKs or

106   pharmacokinetic/pharmacodynamic (PK/PD) analysis. A publication was excluded if: (1) it

107   was a review or only focused on the methodology, algorithm, or software considerations; (2) it

108   was published in a non-English language; and (3) the information on methodology or

109   pharmacokinetics was insufficient.

110   **2.2 Data Extraction**

111   The following information was extracted from the included articles: (1) the characteristics of

112   the target population (patients or healthy subjects) and their demographics (e.g. age, weight

113   range, and sex); (2) the study design (e.g. type of study, number of participants and collected

114   samples, sampling design, dosage regimens, and LEV formulations); and (3) the information

115   on PPK analyses such as data analysis software, structural models, between-subject (BSV)

116   variability and residual unexplained variability (RUV), parameter estimates, covariates, and

117   model evaluation approaches.

118   **2.3 Comparison of Studies**

119   Patient characteristics, population analysis strategies, pharmacokinetic parameters, and the

120   screened covariates of each study were summarised in a tabular format. The concentration-time

121   profiles of neonates (3 kg, postmenstrual age [PMA] 40 weeks), children (30 kg, 10 years), and

122   adults (70 kg, 40 years), for 20 mg/kg LEV were plotted according to the established PPK

123   model and study cohorts in each study. The serum creatinine (Cr) was set to 0.5 mg/dL for

124   neonates and the estimated glomerular filtration rate (eGFR) was set to 90 mL/min/1.73 m^2 for

125   children and adults. The patients were assumed to have received monotherapy and reached a

126   steady state. The sex was set to male.

127   The effect of significant covariates for clearance (CL) in each study was summarised using

128   a forest plot, in which, a less than 20% change in CL was not regarded to have clinical relevance.

129   The effect of each covariate on CL is displayed by the ratio of CL in the range of each covariate

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130 dividing the typical CL value in each study. For binary covariates such as sex, 0 and 1 were

131 used. For continuous covariates included only in one model, we used their minimum and

132 maximum values in the model. For continuous covariates included in several models, we scaled

133 them to the same range for comparison as follows: weight was scaled into three groups

134 including neonates (1–10 kg), children (16–40 kg), and adults (40–100 kg). The range of eGFR

135 was set as 30–100 mL/min/1.73 m^2. The daily dose of LEV was set as 500–3000 mg.

136

3. Results

3.1 Study Identification

139 A total of 143 and 79 studies were identified from the PubMed and Embase database searches,

140 respectively. One additional study was identified via the reference list of the selected articles.

141 After the removal of duplicates, 184 studies were screened. Several screened studies were then

142 disqualified, according to the aforementioned exclusion criteria. Eighteen full-text articles were

143 assessed for eligibility. Among these, three were excluded because of missing PPK parameter

144 estimates, and one was excluded because its data were reported in other articles. Finally, 14

145 studies were included in the review for further analysis. The PRISMA diagram of study

146 identification is presented in Fig. 1.

3.2 Study Characteristics

148 All included studies were published between 2007 and 2020. The characteristics of each

149 study are summarised in Table 1. Sneck et al. [13] enrolled only healthy subjects, Pigeolet et

150 al. included both patients and healthy subjects [14], and the other studies were conducted in

151 patients with epilepsy [15-26]. Eight of the fourteen studies enrolled paediatric patients [15, 17,

152 18, 20, 21, 24-26]; 2 studies were conducted in neonates [18, 21], 4 studies in children less than

153 18 years of age [15, 20, 25, 26], and 2 studies included both children and adults [17, 24]. Three

154   study only enrolled adults [13, 14, 19], and the other three studies included elderly patients of

155   over 70 years [16, 22, 23].

156   The PPK model developed by Karatza et al. [19] and Papa et al. [22] were built using

157   Monolix software and other models were built using NONMEM software. The LEV PK for

158   oral formulations was described with a one-compartment model with first-order absorption and

159   elimination, and for injections was described with a one- or two- compartment model with first

160   order elimination. Two studies conducted in neonates [18, 21], three in children [20, 26], and

161   five in adults were based on sparse sampling data from the routine clinical TDM settings [16,

162   17, 19, 22, 23], and other four studies included intensive sampling data [13-15, 25]. The number

163   of participants in each study ranged from 7 to 524, with LEV observations per individual

164   ranging from 1 to 10. The LEV doses ranged between 4.5 and 130 mg/kg. High-performance

165   liquid chromatography, high-performance liquid chromatography with tandem mass

166   spectrometry, and gas chromatography were employed as LEV bioassay methods. The lowest

167   limit for quantitative assay ranged between 0.1 and 3 μg/mL.

168   **3.3 Comparison of Studies**

169   Two PPK studies were conducted in neonates [18, 21]. For neonates (PMA 40 weeks, 3 kg),

170   the CL estimated by Jung et al. [18] was 0.043 L/h/kg, similar to 0.049 L/h/kg estimated by

171   Lima-Rogel et al. [21]. However, the V estimated by Jung et al. [18] was much higher than that

172   by Lima-Rogel et al. [21] (1.07 vs 0.65 L/h/kg).

173   Most studies conducted in children and adults displayed similar concentration-time profiles,

174   as shown in Fig. 2b and 2c. However, the model developed by Wang et al. [26] showed a

175   considerably higher trough concentration (C_{trough}) than the others, and this could be explained

176   by the fact that the CL estimated by Wang et al. [26] was considerably lower than that estimated

177   in the other studies conducted in children (30 kg, 10 years) (0.038 vs 0.067–0.079 L/h/kg) [17-

178   19, 21].

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179   For neonates (3 kg, PMA 40 weeks), children (30 kg, 10 years), and adults (70 kg, 40 years),

180   the estimated median (range) of CL was: 0.046 (0.043–0.049) L/h/kg for neonates, 0.074

181   (0.038–0.079) L/h/kg for children, and 0.054 (0.039–0.061) L/h/kg for adults. The median CL

182   in neonates and adults was lower than that in children. On the contrary, the V was determined

183   as: 0.86 (0.65–1.07) L/kg for neonates, 0.65 (0.40–0.75) L/kg for children, and 0.60 (0.42–0.93)

184   L/kg for adults. The V for neonates was higher than that for children and adults.

185   The aim of almost all included PPK studies was to identify the potential covariates to describe

186   the BSV of LEV pharmacokinetics, except for that of Papa et al. [22], in which no covariates

187   were investigated because of limited patient numbers. The covariate screening process is

188   summarised in Table 2. All covariates that were investigated and retained in the final model

189   are summarised in Fig. 3. The most frequently screened covariates included weight, eGFR, co-

190   administered medication, sex, and age. The covariates identified for CL included weight, eGFR,

191   co-administered medication, daily dose, sex, Cr, and PMA.

192   Nine of the fourteen studies indicated that weight is associated with the CL of LEV [14, 15,

193   17, 18, 20, 23-26]. Four studies [13, 16, 19, 21], in contrast, found no relationship between

194   weight and CL, but an association between eGFR and CL. Weight had a significant influence

195   on CL in all three age groups (Fig. 4). Moreover, the eGFR could explain the BSV of CL in

196   eight studies [13, 14, 16, 17, 19, 21, 23, 25], five of which showed the clinical significance of

197   an influence on CL larger than ± 20% [13, 16, 17, 19, 23]. According to these studies, in

198   patients with renal impairment (eGFR: 30 mL/min/1.73 m^2), the CL was 44% (12.5%-70.5%)

199   lower than that in patients with median renal function in each study.

200   Three studies reported that the co-administration of enzyme-inducing antiepileptic drugs,

201   such as carbamazepine and phenobarbital, increased the CL by 9%–22%, [14, 24, 25], whereas

202   co-administration with VPA decreased it by approximately 18.8% [14]. However, these co-

203   medications may not have any clinical significance, as the change in CL was found to be less

204   than 22%. Three studies identified that the daily dose could influence the CL [13, 14, 25]. One

205   study showed that females had 10.4% lower CL than males [14]. For neonates, the PMA and

206   Cr were found to significantly affect the CL in one study [18].

207   In all studies included, the BSV was described by exponential models. The median (range)

208   of BSV is as follows: CL, 19.9% (12.5%–43.6%) [n = 14]; V, 17.6% (10.5%–66.2%) [n = 12];

209   and Ka, 100% (32.7%–117%) [n = 7]. The RUV was commonly described by the proportional

210   models to range from 11.49% to 34.3%; a higher RUV was reported by the study in neonates

211   than in other studies [18]. One study showed that the RUV in patients with epilepsy was

212   considerably higher than that in healthy subjects (27.5% and 16.6%, respectively) [14].

213   All models were internally evaluated. The most frequently used method was goodness-of-fit

214   plots, which showed the closeness between prediction and observation. Only three studies

215   performed external evaluation and showed acceptable predictability [16, 24, 26].

216   Nine studies performed a model-based simulation to display the effects of covariates and

217   propose dosing regimens [13-17, 19, 21, 24, 25]. The influence of age, weight, race, and eGFR

218   on LEV clearance, area under the concentration-time curve, C_{trough}, and C_{max} were investigated.

219   Weight and eGFR were found to have significant influences on dose recommendation. For

220   children, Toublanc et al. (2008) [25] recommended that the dosage should be differentiated as

221   per body weight: 10 mg/kg for children less than 20 kg; 250 mg twice daily for children

222   between 20 and 40 kg, and 500 mg twice daily for children more than 40 kg. For adults,

223   Hernández-Mitre et al. [16] recommended to adjust the dosage according to eGFR to achieve

224   the trough LEV concentrations between 12 and 46 μg/mL.

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4. Discussion

LEV is one of the most widely used AEDs. There has been a continued interest in studying the LEV pharmacokinetics from the past few decades, and several PPK studies have been reported to identify the sources of variability. This is the first review to summarise the knowledge concerning the population pharmacokinetic modelling of LEV.

All studies conducted in adult patients showed similar concentration-time profiles for patients with the same demographic characteristics. Moreover, two population studies investigated the ethnic variance for LEV, and found no obvious difference [14, 24]. Toublanc et al. (2014) [24] developed a PPK model based on Japanese patients and extrapolated it to North American patients through an external evaluation; the model showed satisfactory predictive performance. Pigeolet et al. [14] enrolled Japanese, European, and North American patients to conduct a PPK analysis and did not find any significant difference among these sub-populations. However, Wang et al. [26] showed a lower clearance in Chinese children than in Japanese, European, and North American sub-population. This difference warrants further investigation.

The pharmacokinetics of LEV showed large differences between children and adults. The children showed a higher CL and a lower V per kilogram body weight than the adults with the same dosage per kilogram bodyweight. The difference in CL between children and adults may be attributed to the decrease in blood flow, increase in body fat/lean mass ratio, and decrease in total body water owing to ageing. One study reported that the CL of LEV rapidly increased after birth and decreased during ageing, which is similar to the growth tendency of renal function [27]. The renal function increases rapidly during the first 2 to 3 years of life and then decreases with ageing in proportion to the physiological function decrease [28]. As LEV is mainly eliminated by the kidney, and children showed a higher renal function than adults, the alternation in renal function during ageing may account for the difference in CL between

250   children and adults [29, 30]. Thus, a higher dosage per weight is required in children than in

251   adults for the same trough concentration.

252   As LEV is mainly eliminated by the kidney (66%), renal function indicators, such as eGFR

253   and Cr, may influence the CL of LEV drastically [6]. Karatza et al. [19] found that the CL of

254   LEV decreased by approximately 27.6% for patients with renal insufficiency (60 mL/min/1.73

255   m^2), and 58.3% in patients with renal impairment (30 mL/min/1.73 m^2) compared with

256   individuals with a normal renal function (90 mL/min/1.73 m^2). Jung et al. [18] found that the

257   CL of LEV may decrease by approximately 37% in neonates, with an increase in Cr by 30%.

258   Consequently, the dosing regimen for patients with renal impairment needs to be adjusted.

259   Three studies identified that the daily dose affected the CL of LEV, which may indicate a

260   non-linear elimination of LEV [13, 17, 25]. Toublanc et al. (2008) [25] and Ito et al. [17] found

261   higher dosage increased the CL. On the contrary, Snoeck et al. found higher dosage could

262   decrease the CL [13]. This influence may result from the dose adjustment in clinical settings,

263   where a higher dosage was adjusted for patients with a higher CL [31]. Further exploration of

264   the potential non-linear PK of LEV is still needed.

265   Only 2.5% of LEV is metabolised by the hepatic cytochrome P450 system [6]. Therefore,

266   the CL of LEV may be less affected by the CYP enzyme inducers or inhibitors. Yet, three PPK

267   studies showed that co-administration with enzyme-inducing antiepileptic drugs, such as

268   carbamazepine and phenobarbital, could increase the CL of LEV by 9%–22% [14, 24, 25]. The

269   possible enzyme induction effect requires further investigation.

270   Moreover, Pigeolet et al. [14] found that the co-administration of LEV and VPA decreased

271   the CL of LEV by 18.8% in their PPK analysis. This finding was consistent with the

272   observations of Perucca et al. and May et al. [7, 32] that VPA could influence the CL of LEV

273   in classical PK studies. However, Coupez et al. [33] found that VPA could not alter the

274   pharmacokinetics of LEV during *in vitro* and *in vivo* studies. VPA is the inhibitor of epoxide

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275   hydrolase and the CYP2C isoenzymes, none of which are involved in the pharmacokinetics of

276   LEV. Thus, the mechanism of VPA and LEV interaction remains to be clarified in future

277   studies.

278   Ten studies reported that the V has a significant relationship with weight [13-15, 17, 18,

279   20, 21, 23-25], except three studies fixed it to be 12.5, 34.7, and 33L, respectively [19, 22, 26]

280   and one study found that the V has a significant relationship with body surface area (BSA) [16].

281   Pigeolet et al. [14] found that the V was 13.9% lower in healthy subjects than in patients with

282   epilepsy. Moreover, in this study, V was found to decrease by 23.4% in patients co-

283   administered with VPA. However, its mechanism remains uncertain.

284   Four studies reported a PK/PD analysis and their findings were not consistent [15, 19, 20,

285   34]. Chhun et al. [15] performed the exposure-response analysis for LEV, wherein the patients

286   were classified into two groups (seizure-free for at least 3 months or not). The C_{trough} showed

287   no difference between the groups. In the other study, Snoeck et al. [34] utilised a model to

288   predict the reduction in seizure frequency with PK of LEV, and indicated a clear relationship

289   between LEV dose and effect. Kim et al. [20] found Weibull distribution could best describe

290   the time to seizure recurrence with LEV administration, but no significant covariates were

291   identified. Karatza et al. [19] found a strong PK/PD linkage between LEV concentrations and

292   seizure recurrence. In this study, patients with a higher daily dose and higher eGFR were more

293   likely to have a seizure recurrence, but only eight patients were recruited [19]. Thus, further

294   prospective PK/PD studies of LEV with larger samples should be conducted to clarify the

295   exposure-response relationship.

296   Owing to the linear pharmacokinetics, low protein binding, and better safety profile of

297   LEV, it has been increasingly used off-label in the treatment of neonatal seizures [35].

298   Accumulating evidence on the safety and efficacy of LEV in neonatal seizures support its use

299   as a second-line therapy [36]. So far, two PPK studies have been conducted in neonates, using

300   either an oral solution or IV injection formulation [18, 21]. The CL for neonates has been found

301   to be highly influenced by Cr, which should be considered for dose adjustment for neonates.

302   Besides, the RUV in models for neonates was the highest among all the included studies. The

303   large differences between neonates may be owing to the physiological differences such as total

304   body water-to-fat ratios, gastrointestinal motility, drug-metabolising enzyme activity, and renal

305   function [37, 38]. Further studies are still needed to identify influential factors and describe the

306   variability.

307   LEV shows a good foetal safety profile and has been widely used for pregnant women

308   with epilepsy [39-42]. However, the CL of LEV is higher in pregnant women than in non-

309   pregnant individuals, which could lead to the failure of seizure control [8, 43]. Thus, the TDM

310   of LEV in pregnant patients is necessary to maintain the appropriate concentration [44].

311   However, the data reported for LEV in pregnant women are insufficient. As PPK modelling

312   can help investigate the pharmacokinetic characteristics in special populations from sparse

313   samples, it offers an appropriate approach for dose individualisation in pregnant women, and

314   it has been used for individualised lamotrigine therapy in pregnant women [45]. Thus, further

315   PPK studies are required to characterise LEV pharmacokinetics in pregnant women in the

316   future.

317

5. Conclusions

319   The PPK studies of LEV were systematically reviewed. The pharmacokinetics of LEV

320   differed between children and adults, such that children show a higher CL and a lower V than

321   adults following the same dosage per kilogram body weight. The review establishes that LEV

322   dose individualisation should be dependent on the body size and renal function of patients.

323 Further PPK studies are required in neonates and pregnant women to establish the LEV

324 pharmacokinetic profile.

325

Declarations

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Competing interests

Zi-ran Li, Chen-yu Wang, Xiao Zhu, and Zheng Jiao declare that they have no conflict of interest.

Ethics approval

Not applicable.

Consent to participate

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Consent for publication

Not applicable.

Availability of data and material

Code availability

Not applicable.

Author contributions

Zi-ran Li, Chen-yu Wang, and Zheng Jiao designed the review and planned the work that led to the manuscript. Zi-ran Li and Chen-yu Wang performed the literature search and data analysis. Zi-ran Li, Xiao Zhu, and Zheng Jiao drafted and revised the manuscript. All authors approved the final version of this manuscript.

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467 **Table 1. Characteristics of population pharmacokinetic studies included in the systematic review.**

Study (publication year)	Type of study	Country	Number of subjects (M/F)	Number of sample size	Sampling time	Age Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Formulation	Daily Dose Mean ± SD Median [Range]	LEV assay [LOQ]
Pigeolet et al. (2007) [14]	Retrospective	Japan, Western[a]	Japan:213 (136/77) Western:311 (206/105)	Japan: 2041 Western: 3367	IS[b] and C_{trough}	Japan: 29 [16-55] years western: 38 [16-71] years	japan: 60 [40-107] western: 77 [42-141]	Tablet	[250-5000] mg	LC & GC [0.5 μg /mL]
Snoeck et al. (2007) [13]	Prospective	Belgium	30 (18/12)	NR	IS[c]	38 ± 9	71 ± 12	IV injection	[1500-4000]mg	GC [0.5 μg/mL]
Toublanc et al. (2008) [25]	Retrospective	NR	228 (120/108)	2319	IS[d] and C_{trough}	9.8 [0.20-18] years	32 [6-89]	Tablet or oral solution	[10-60] mg/kg	GC [0.5 μg/mL]
Chhun et al. (2009) [15]	Prospective	NR	44 (86/84)	170	IS[e] and C_{trough}	11 [4.6-16.6] years	33 [16-65]	Tablet	10/20/40 mg/kg	HPLC [1 μg/mL]
Wang et al. (2012) [26]	Prospective	China	311 (160/151)	418	SS[f]	6.34 [0.5-14] years	25.17 [5-70]	Tablet	655.17 [250–2000] mg	HPLC [1 μg/mL]
Toublanc et al. (2014) [24]	Retrospective	Japan	259 (137/122)	1833	SS[g]	26.8±13.5 25.6 [4.3-55.4] years	51.6±17.2 51.5 [13.8-107]	Tablet or oral solution	[1000-3000] mg or 20-60 mg/kg	NR
Ito et al. (2016)[17]	Retrospective	Japan	225 (112/113)	583	SS[h]	38 [1-89] years	53.8 [9.5-109]	NR	1200 [62.5-3000] mg	LC-MS/MS [0.2 μg/mL]
Rhee et al. (2017)[23]	Retrospective	Korea	425 (206/219)	483	SS[h]	35.0 [16.0-85.0] years	62.8 [40.0-123.6]	Tablet	[125-4000] mg	NR
Jung et al. (2018) [18]	Retrospective	Korea	18 (11/7)	151	SS[i]	PMA: 47.6 ± 6.63 48.7 [22.3-66.0] weeks	4.3 ± 1.76 4.3 [0.54-10.45]	IV injection or oral solution	30 [20-60] mg/kg	LC-MS/MS [1 μg/mL]
Lima-Rogel et al. (2018) [21]	Prospective	Mexico	20 (11/9)	44	SS[j]	CGA: 39.8 [30-43] weeks	2.9 [0.9-3.75]	IV injection	20 [10-50] mg/kg	HPLC [3 μg /mL]
Kim et al. (2018) [20]	Prospective	Korea	37 (18/19)	107	SS[k]	6.6 ± 5.3 [0.08-15.1] years	18 [3.0-87.5]	IV injection	26.6 [20-30] mg/kg	LC-MS/MS [0.1 μg/mL]
Karatza et al. (2020) [19]	Prospective	Greece	8 (5/3)	24	SS[l]	45 [38-53] years	81 [54-98]	Tablet	2000 [1000-3000] mg	LC-MS/MS [0.46 μg/mL]
Hernández-Mitre et al. (2020) [16]	Prospective	Mexico	74 (34/40)	269	SS[m]	40 [18-94] years	65 [42-140]	Tablet	[250-2000] mg	HPLC NR
Papa et al. (2020) [22]	Prospective	Uruguay	7 (2/5)	NR	C_{trough}	81 [52-86] years	NR	SC injection	[1000-3000]mg	HPLC NR

23

CGA: corrected gestational age; GC: gas chromatograph; HPLC-UV: high-performance liquid chromatography with ultraviolet detector; HPLC: high-performance liquid chromatography; IV: intravenous; LC-MS: liquid chromatograph mass spectrometer; LC-MS/MS: liquid chromatograph mass spectrometer or mass spectrometer; NR: not reported. C_{trough}: trough concentration. PMA: postmenstrual age:

[a] Western: Europe and the North America.

[b] Intensive sampling: the detailed sampling time was not reported.

[c] Intensive sampling: before infusion, and at time points of 5, 10, 15, and 30 min and 1, 2, 3, 6, 9, 12, and 24 h

[d] Intensive sampling: 0.25, 0.5 1-7, 9, 12, 16, 24 h post dose receiving a single dose.

[e] Intensive sampling: group A (0.33, 1.33 2, 3 h); group B (0.5, 1.5 2, 4 h); group C (0.66, 1.66, 3, 4 h).

[f] Sparse sampling: 1-13 h post dose.

[g] Sparse sampling: at any time.

[h] Sparse sampling: not reported.

[i] Sparse sampling: 6-12 h post dose for 12 h dosing interval; 9-23 h post dose for 24 h dosing interval.

[j] Sparse sampling: 2-10 min, 4-8 h and 24 h after infusion.

[k] Sparse sampling: 0-3 min, 20-80 min and 3.5-6.5 h after infusion.

[l] Sparse sampling: 2, 5, and 12 h post dose.

[m] Sparse sampling: a mean of 4 samples between 15 min to 12 h post dose.

Table 2. Model strategies and final pharmacokinetic parameters of included studies in the systematic review.

Study (publication year)	Estimation method	Fixed effect parameters		Between-subject variability (%)	residual unexplained variability	Internal validation	External validation (N=number of samples)	Simulation target
Pigeolet et al.(2007) [14]	FOCE-I	K_a	2.44 (fed) 4.80 (fasted)	108	patients: 27.5%	GOF	NR	AUCs, CL, V, C_{trough}, concentration-time profiles
		CL	$4.02 \times (WT/70)^{0.268}$ $\times (eGFR/110)^{0.122}$ $\times$ (1 for male; 0.896 for female) $\times$ (1.09 for IND; 0.812 for VPA; 1 for others)	19.5	healthy subjects: 16.6%			
		V	$52.7 \times (WT/70)^{0.952}$ $\times$ (1 for patients with epilepsy; 0.861 for healthy subjects) $\times$ (0.766 for VPA; 1 for others)	11.8				
Snoeck et al. (2007) [13]	FOCE-I	CL	$4.16 \times (eGFR/124)^{0.857}$ $\times (DD/2000)^{-0.185}$	12.5	14.7%	GOF	NR	AUCs, C_{max}, C_{trough}
		Vd_{ss}	$43.6 \times (WT/72.5)^{1.07}$	10.5				
		K_{12}	1.09	104				
		K_{21}	1.92	/				
Toublanc et al.(2008) [25]	FOCE	K_a	$1.46 \times (AGE/10)^{0.27}$	100, 112[a]	30%	GOF	NR	C_{trough}
		CL	$2.17 \times (WT/30)^{0.64}$ $\times (DD/500)^{0.0443}$ $\times (eGFR/100)^{0.111}$ $\times$ (1.22 if co-administered with CBZ, PHT, PB, or PD)	19				
		V	$21.5 \times (WT/30)^{0.901}$	19				
Chhun et al.(2009) [15]	FOCE-I	K_a	3.83	117	18.90%	GOF, NPDE, VPC	NR	AUCs, CL, $t_{1/2}$, C_{trough}
		CL	$2.47 \times (WT/33)^{0.89}$	24.3				
		V	$21.9 \times (WT/33)^{0.93}$	16.3				
		Tlag	0.283	COR=16.7				
Wang et al.(2012) [26]	FOCE	K_a	1.56	/	16.70%	GOF	N=50	NR
		CL	$1.04 \times (WT/25)^{0.563}$	19.5				
		V	12.1	16.3				
Toublanc et al.(2014) [24]	FOCE-I	K_a	2.56	85.8	18.90%	VPC	N=228	AUCs, C_{max}, C_{trough}
		CL	$2.1 \times (WT/32)^{0.75}$ $\times$ (1.22 if co-administered with IND)	19.9 COR = 13.5				
		V	$20.4 \times (WT/32)$	12.2				
Ito et al.(2016) [17]	FOCE-I	K_a	0.464	65.9	30.6%	GOF	NR	CL
		CL	$4.33 \times (WT/70)^{0.75}$ $\times (eGFR/100)^{0.638}$ $\times (1 + 0.175 \times (DD/(WT^{0.75} \times 59.3)))$	17.9				
		V	$0.753 \times WT$	/				

Table2. (Continued)

Study (publication year)	Estimation method	Fixed effect parameters		Between-subject variability (%)	residual unexplained variability	Internal validation	External validation (N=number of samples)	Simulation target
Rhee et al.(2017) [23]	FOCE-I	K_a	2.44	/	0.395 ng/mL	GOF, bootstrap	NR	NR
		CL	$3.9 \times (WT/70)^{0.70} \times (eGFR/90)^{0.44}$	19.9				
		V	$65.3 \times (WT/70)$	60.8				
Jung et al.(2018) [18]	FOCE-I	K_a	10	/	34.3%	GOF, VPC	NR	NR
		F	0.775	/	1.266 µg/mL			
		CL	$0.316 \times (WT/4.3)^{0.75} \times [PMA^{3.391}/(43.52^{3.391} + PMA^{3.391})]/0.594 \times e^{-1.226 \times (Cr-0.25)}$	32				
		V	$4.627 \times (WT/4.3)$	66.2				
Lima-Rogel et al. (2018) [21]	FOCE	CL	$0.47 \times eGFR^b$	36	13%	GOF, VPC	NR	Maintaining dose regimens
		V	$0.65 \times WT$	22				
Kim et al. (2018) [20]	FOCE-I	CL	$1.44 \times (WT/18)^{0.98}$	16.4 COR=61	19%	GOF, VPC	NR	NR
		V	$8.55 \times (WT/18)^{0.87}$	22.4				
Karatza et al. (2020) [19]	SAEM	K_a	0.616	32.7	16%	GOF, VPC, NPDE	NR	concentration-time profiles
		CL	$3.26 \times (eGFR/139)^{0.795}$	27.4				
		V	34.7	15.9				
Hernández-Mitre et al. (2020) [16]	FOCE-I	K_a	3.63	139.6	11.49%	Bootstrap,	N=98	C_{trough}
		CL	$2.74 \times (eGFR/96.2)^{0.588}$	43.6				
		V	$29.7 \times (BSA/1.68)^{2.85}$	30.4				
Papa et al. (2020) [22]	SAEM	CL	2.51	42	10.5 mg/L	NR	NR	NR
		V	33	/				

K_a: absorption rate constant (h^{-1}); F: bioavailability; Tlag: absorption lag time (h); CL: apparent clearance (Lh^{-1}); V: apparent volume of distribution (L); Vd$_{ss}$: steady-state distribution volume (L); K_{12}: inter-compartment rate constants from central to peripheral compartment (h^{-1}); K_{21}: inter-compartment rate constants from peripheral to central compartment (h^{-1}); WT: body weight (kg); AGE: age of patients (year); PMA: postmenstrual age (week); DD: daily dose (mg/day); eGFR: estimated glomerular filtration rate (mL/min/1.73m^2); IND: enzyme-inducing antiepileptic drugs; VPA: valproate acid; CBZ: carbamazepine; PHT: phenytoin; PB: phenobarbital; PD: primidone; Cr: creatinine (mg/dL); COR: covariance between CL and V; GOF: goodness-of-fit plot; VPC: visual predictive check; NPDE: normalized prediction distribution errors; AUCs: area under the plasma concentration-time curve; C$_{trough:}$ trough concentration (µg/mL); C$_{max}$: peak plasma concentration (µg/mL); t$_{1/2}$: elimination half-life (h);

* NR: not reported.

*a between-occasion variability;

*b the unit of eGFR was L/h in this model. It was calculated by $K \times Height$ (cm)$/Cr$ (mg/dL), in which K was set 0.45, height was set 50 cm; BSA was calculated by $\sqrt{(height(cm) \times weight(kg))}/3600$.

Table 3. List of tested and significant covariates in the models.

Study (publication year)	Tested covariates Demographic	Laboratory examination	Co-administration	Covariate selection criteria Forward inclusion	Backward elimination	Significant covariates K_a	CL	V
Pigeolet et al. (2007) [14]	Weight, Height, BMI, BSA, Sex, Race, Subject Type[a]	eGFR, Serum Creatinine	AEDs, Benzodiazepine	$P < 0.05$	$P < 0.005$	NR	Weight, eGFR, Sex, IND, VPA	Weight, Subject Type, VPA
Snoeck et al. (2007) [13]	Age, Weight, Sex, Daily Dose	eGFR	NR	$P < 0.05$	$P < 0.005$	NR	eGFR, Daily Dose	Weight
Toublanc et al. (2008) [25]	Age, Weight, BSA, BMI, Sex, Race, Daily Dose	eGFR	Inducer, Inhibitor, Benzodiazepine	$P < 0.05$	$P < 0.005$	Age	Weight, eGFR, Daily Dose, IND	Weight
Chhun et al. (2009) [15]	Age, Weight, Sex	eGFR	NR	$P < 0.05$	$P < 0.01$	NR	Weight	Weight
Wang et al. (2012) [26]	Age, Weight, Daily Dose	NR	VPA, LTG, CBZ, OXC, TPM	$P < 0.005$	NR	NR	Weight	NR
Toublanc et al. (2014) [24]	Age, Weight, Formulation	NR	Neutral, Inducer, Inhibitor, A combination of inducer and inhibitor	$P < 0.05$	$P < 0.001$	NR	Weight, IND	Weight
Ito et al. (2016) [17]	Age, Weight, Sex, Daily Dose	eGFR, ALT, AST	AEDs	$P < 0.01$	$P < 0.005$	NR	Weight, eGFR, Daily Dose	Weight
Rhee et al. (2017) [23]	Age, Weight, Height, Sex	eGFR, Serum Creatinine, AST, ALT , Albumin, Total bilirubin	VPA, LTG, CBZ, OXC, TPM, Phenytoin, Phenobarbital, Pregabalin, Zonisamide, Clobazam	$P < 0.05$	$P < 0.001$	NR	Weight, eGFR	Weight
Jung et al. (2018) [18]	PMA, GA, Weight, Apg1, Apg5	Serum Creatinine	NR	$P < 0.01$	$P < 0.001$	NR	Weight, PMA, Creatinine	Weight
Lima-Rogel et al. (2018) [21]	PNA, GA, CGA, Weight, Height, BSA, Apgar Score, Sex	eGFR, Serum Creatinine	NR	$P < 0.05$	$P < 0.001$	NR	eGFR	Weight
Kim et al. (2018) [20]	Age, Weight, Height, Sex	eGFR	NR	$P < 0.05$	NR	NR	Weight	Weight
Karatza et al. (2020) [19]	Age, Weight, Height, Daily Dose	eGFR	NR	$P < 0.01$	NR	NR	eGFR	NR
Hernández-Mitre et al. (2020) [16]	Age, Weight, Height, BSA, BMI	eGFR, Serum Creatinine	Inducer, Inhibitor	$P < 0.05$	$P < 0.01$	NR	eGFR	BSA
Papa et al. (2020) [22]	NR	NR	NR	NR	NR	NR	NR	NR

BMI: body mass index; BSA: body surface area; CGA: corrected gestational age; PMA: postmenstrual age; PNA: postnatal age; GA: gestational age; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; IND: enzyme-inducing antiepileptic drugs; AEDs: antiepileptic drugs; VPA: valproate acid; LTG: lamotrigine; CBZ: carbamazepine; OXC: oxcarbazepine; TPM: topiramate; Apg1: Apgar score = 1; Apg5: Apgar score = 5; NR: not reported. Inducer: enzyme-inducing AEDs as carbamazepine, oxcarbazepine, primidone, phenytoin and phenobarbital; Inhibitor: enzyme-inhibiting AEDs as valproate acid;

[a] Subject Type: Healthy subject or patients with epilepsy;

Figure legends

Fig. 1 PRISMA flow diagram for the identification of LEV PPK studies.

Fig. 2 Concentration-time profiles of LEV at steady state for neonates (a), children (b), and adults (c) in retrieved studies.
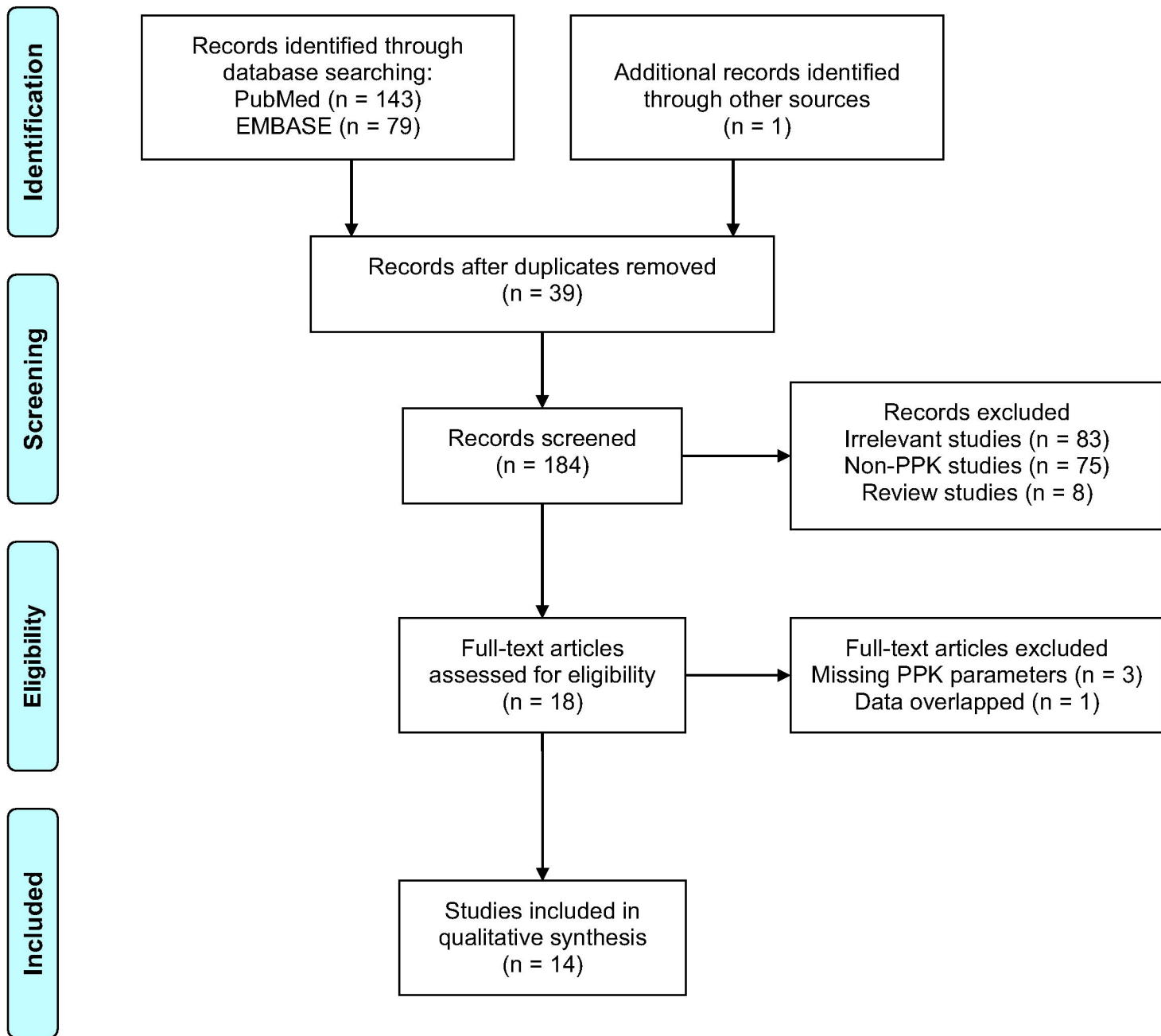
The solid line represents median of the simulated concentration-time profile. The light shadows represent the 10th-90th percentiles of the simulated concentration-time profiles. The estimated glomerular filtration rate (eGFR) was set to 90 mL/min/1.73 m^2 for children and adults. The creatinine (Cr) for neonates was set to 0.5 mg/dL. All patients were assumed to be male receiving LEV monotherapy at a dose of 20 mg/kg. PMA: postmenstrual age.

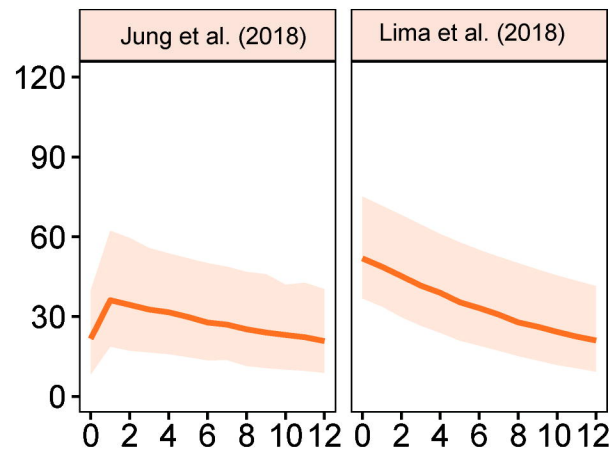**Fig. 3 Investigated and identified covariates for clearance of LEV.**

eGFR: the estimated glomerular filtration rate; BSA: body surface area; IND: co-administration with enzyme-inducing antiepileptic drugs; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; GA: gestational age; VPA: co-administration with valproate acid; CGA: corrected gestational age; PNA: postnatal age; PMA: postmenstrual age.

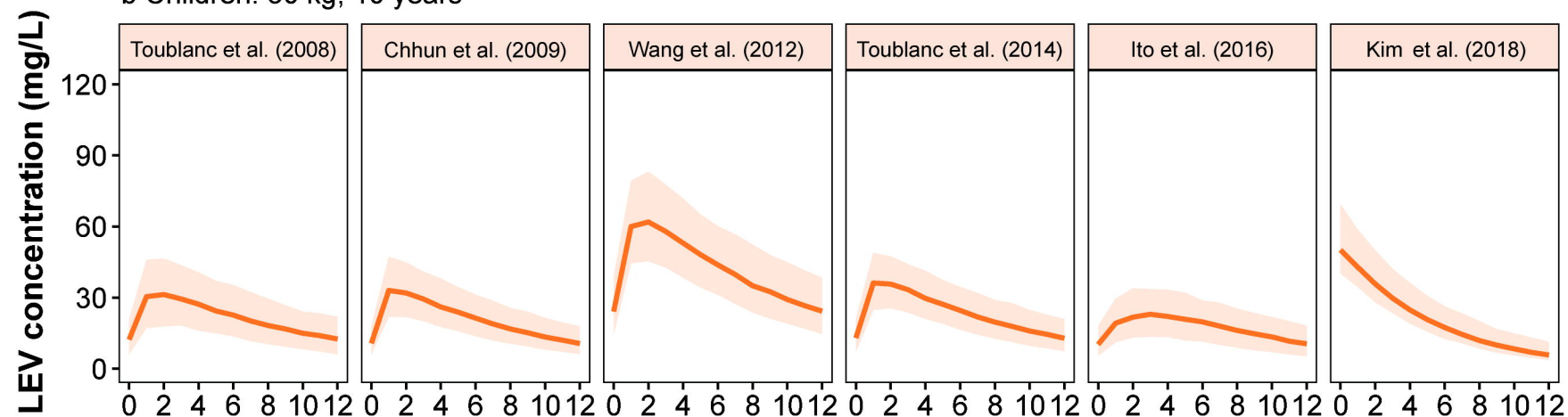**Fig. 4 Covariate effect on the clearance of LEV.**

The horizontal bars represent the covariate effect on clearance in each study. The typical value of clearance in each study was considered to be 1. The effect of each covariate for clearance is displayed by the ratio of clearance in the range of each covariate to the typical clearance value. The shaded gray area ranges from 0.8 to 1.25. eGFR: the estimated glomerular filtration rate; IND: co-administration with enzyme-inducing antiepileptic drugs; VPA: co-administration with valproate acid; PMA: postmenstrual age; Y: yes, co-administration; N: no, not co-administration; M: male; F: female.

a Neonates: 3 kg, PMA 40 weeks

Jung et al. (2018) | Lima et al. (2018)

b Children: 30 kg, 10 years

Toublanc et al. (2008) | Chhun et al. (2009) | Wang et al. (2012) | Toublanc et al. (2014) | Ito et al. (2016) | Kim et al. (2018)

c Adults: 70 kg, 40 years

Pigeolet et al. (2007) | Snoeck et al. (2007) | Toublanc et al. (2014) | Ito et al. (2016) | Rheea et al. (2017) | Karatza et al. (2020) | Hernández et al.(2020) | Papa et al. (2020)

LEV concentration (mg/L)

Time (h)