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Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults

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ABSTRACT: *Purpose*. Gastric emptying (GE) is often reported to be slower and more irregular in premature neonates than in older children and adults. The aim of this study was to investigate the impact of age and other covariates on the rate of GE. *Methods*. The effect of age on the mean gastric residence times (MGRT) of liquid and solid food was assessed by analysing 49 published studies of 1457 individuals, aged from 28 weeks gestation to adults. The data were modelled using the nonlinear mixed-effects approach within NONMEM version 7.2 (ICON, Dublin, Ireland), with evaluation of postnatal age, gestational age and meal type as covariates. A double Weibull function was selected as a suitable model since it could account for the typical biphasic nature of GE. *Results*. Age was not a significant covariate for GE but meal type was. Aqueous solutions were associated with the fastest emptying time (mean simulated gastric residence time of 45 min) and solid food was associated with the slowest (98 min). *Conclusions*. These findings challenge the assertion that GE is different in neonates, as compared with older children and adults due to age, and they reinforce the significance of food type in modulating GE. © 2015 The Authors. *Biopharmaceutics & Drug Disposition* Published by John Wiley & Sons Ltd.

Key words: gastric emptying; neonatal gut; paediatric gastroenterology; infant gut

Introduction

The stomach controls the rate at which nutrients and xenobiotics (including drugs) reach the duodenum and are absorbed into the systemic circulation. In the fasted state, gastric motility occurs in continuity with the rest of the intestine as part of the migrating motor complex (MMC) [1]. In the fed state, gastric motility is highly dependent on meal composition [1], and may be slowed by diseases such as diabetes [2], in people with high body mass index (BMI) [3] and in the elderly [4].

Scintigraphy (typically using a solid meal labelled with ^{99m}Tc-sulphur colloid or a liquid meal labelled with indium) is generally considered to be the gold standard method for measuring gastric emptying [5,6], and correlations have been established with results of the ^{13}C-acetate breath test [7], PEG dilution [8], acetaminophen (paracetamol) kinetics [8] and ultrasound [3,9]. Gastric emptying profiles are often noted to be biphasic, especially after a solid and/or high-fat meal, due

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to inhibitory feedback from the small intestine [1]. The first phase is indicated either by a lag time [10–12] or an initial faster process [4,12,13].

It is often stated that gastric emptying is slower in neonates, especially premature ones, compared with older infants and children [14–19]. This is usually assigned to immaturity of the neuro-regulation of motility, although data on the postnatal development of gastric motility are equivocal. Gastric emptying cycles have been observed in fetuses of 24 weeks gestation [20], and premature neonates born at 30 to 38 weeks' gestation have been shown to have the isolated pyloric pressure wave patterns necessary to coordinate gastric functions including stomach emptying [21]. In addition, stable patterns of slow gastric waves have been reported in premature neonates at 28 to 36 weeks after gestation and starting at postnatal day 3 [22]. However, in term and pre-term infants a 30–40% incidence of normal slow waves (between two and four counts per minute) was found to increase with age to nearly 90% in adults in both the fasting and fed states, indicating significant development of postnatal coordination of gastric emptying [23,24].

Although premature neonates have been noted to be more likely than term neonates to suffer from feed intolerance, regurgitation and gastro-oesophageal reflux, the causes of this may be altered feedback from the proximal small intestine and intolerance to the high fat content of preterm infant formulas rather than any impairment of gastric motility [25–27]. Lange *et al*. found no difference in the half-emptying time between preterm and term infants after a test meal of water [28]. However, Riezzo *et al*. observed a significantly longer half-emptying time at 1 week after birth in preterm infants (28–32 weeks' gestation) compared with preterm neonates born at a later gestational age and term neonates after a meal of formula [18]. No differences in gastric emptying half-life have been observed between older children, adolescents and adults [29]. However, it appears that there have been no studies comparing gastric emptying times between ages ranging from preterm neonates through to adults.

A complication in evaluating whether or not gastric emptying is impaired in term or preterm neonates is that in the fed state the process is known to be strongly influenced by meal type, which may differ depending on the ages of the subjects studied. While older children and adults may be tested using a variety of liquids and solids, neonates can only consume liquid test meals, usually breast milk or formula (and occasionally water or sugar solutions), which confounds comparisons with studies done in older adults and children using solid meals. Liquids are known to empty more rapidly from the stomach than solids and breast milk empties more quickly than formula [13,30,31]. Aqueous solutions empty more quickly than liquids containing fat and/or protein content which, in turn, empty more rapidly than solids [1].

Understanding changes in gastric emptying with age is important both clinically in terms of the pathophysiology of disease and for predicting the absorption of orally administered drugs [32]. Gastric emptying is a primary determinant of the rate at which drugs are presented to the small intestinal mucosa for absorption and, along with a multitude of other age related changes, may influence the design of suitable dosage forms for administration to neonates and infants. This study is part of a wider effort to develop a comprehensive paediatric drug absorption model.

The aim of this study was to investigate the impact of age and other covariates on the rate of gastric emptying. Accordingly, to document a more complete understanding of the impact of development on gastric emptying, a meta-analysis of the literature with respect to studies on preterm neonates through to adults was done using a mixed effect modelling approach.

Methods

Search strategy and data selection

A literature search was undertaken using the PubMed and Embase databases. Keywords were 'gastric emptying' (PubMed) and 'gastric emptying AND neonates' or 'gastric emptying AND pediatrics' with limits (PubMed) or filters (Embase) of 'human' and 'English'. In PubMed, initial searches were conducted in each of the paediatric age groups individually, i.e. 'Newborn: birth–1 month', 'Infant: birth–23 months', 'Pre-school child: 2–5 years', 'Child: 6–12 years', 'Adolescent:

13–18 years', and the adult age categories. The last data search was in June 2014. Some references were also obtained from the bibliographies of published papers.

The inclusion criterion was studies in healthy preterm neonatal through to adult subjects that reported the % remaining of gastric contents at time points after administration of a test meal. Subject groups were excluded if they were obese, receiving drugs affecting GI motility (such as metoclopramide or cisapride), had disease (except for apnoea) and were stated to have regurgitation or vomiting. Paediatric and adult subjects were excluded if they had proven gastro-oesophageal reflux (GOR), but not if referred for testing for suspected GOR. The study database used to obtain the final model comprised 49 studies of 1457 subjects. The final model was validated using an independent dataset comprising 17 studies of 468 subjects. The latter were selected randomly after grouping them for similar age ranges.

Data extraction

The data extracted from the studies consisted of either the mean or median % of a test meal remaining in the stomach at various time points after administration. When not listed in manuscript tables or text, data on the percentage remaining in the stomach after administration of food were retrieved from figures by computer digitalization (Enguage Digitizer, Version 4.1, Free Software Foundation, Inc., Boston, MA).

Model building and selection criteria

The data were modelled using a nonlinear mixed effects approach using NONMEM, Version 7.2 (ICON, Dublin, Ireland) with the first-order conditional estimation method (FOCE) with interaction. The model building process was guided by graphical analysis of goodness of fit plots in Xpose 4 Version 4.3.5 [33] and changes in the Akaike information criterion (AIC) calculated from the objective function values (OFV) obtained from NONMEM and the number of model parameters. Uncertainty in estimated model parameters is indicated by the relative standard error values (RSE) obtained from NONMEM.

Based on visual inspection of the % remaining versus time data, three structural models were tested: namely exponential decay [34], exponential decay with a lag time [34] and a double Weibull function [35]. An advantage of the latter model (Eq. (1)) is the flexibility it provides with respect to describing the relative speed of two emptying phases.

$$GE_{\mathbf{ij}} = (100 - PR_{\mathbf{i}})\cdot e^{-\left(\frac{t_{ij}}{\gamma_{1,i}}\right)^{\beta_{1,\mathbf{i}}}} + PR_{\mathbf{i}}\, e^{-\left(\frac{t_{ij}}{\gamma_{2,i}}\right)^{\beta_{2,i}}} \quad (1)$$

Where GE_{ij} is the percentage of the test meal remaining in the stomach at time t_{ij} for the ith publication at jth time point. The parameters $\gamma_{1,\mathrm{i}}$ *and* $\gamma_{2,\mathrm{i}}$ define the scatter and $\beta_{1,\mathrm{i}}$ *and* $\beta_{2,\mathrm{i}}$ define the shape of the distribution. If the condition $\gamma_{1,\mathrm{i}} < \gamma_{2,\mathrm{i}}$ is satisfied, then the parameter PR_{i} represents the percentage of test meal remaining in the stomach when the emptying study period is complete. The value of PR_{i} was constrained between 0 and 100 by using a logit transformation [36].

Inter-study variability (η_{i}) in the parameters was described using an exponential error model (Eq. (2)).

$$\theta_{\mathrm{i}} = \overline{\theta} \times \exp(\eta_{\mathrm{i}}) \quad (2)$$

The ith study's parameter θ_{i} was assumed to differ from the population mean parameter $\overline{\theta}$ by a value of exp (η_{i}). The value of η_{i} was assumed to have a normal distribution with a mean of 0 and variance of ω^2.

The residual error structure (Eq. (3)) was weighted based on the number of patients represented at each time point and the method used to measure the GE_{ij}, to account for heteroscedasticity and any inaccuracies in the methods.

$$GE_{ij} = \widehat{GE}_{ij} + \frac{\theta_w}{\sqrt{N_{ij} \times T_i}} \times \varepsilon_{ij} \quad (3)$$

Where, $\widehat{GE}_{ij}$ is the model prediction based on the data, θ_{w} is the standard deviation, N_{ij} is the sample size, T_{i} is the test type used to measure the % remaining and $\varepsilon_{\mathrm{ij}}$ is the additive-error component of residual variability. T was given a value of 2 when the data were obtained by scintigraphy and 1 when another method was

used in order to give more weight to scintigraphy. The variance of ε was fixed at 1.

Mean gastric residence times (MGRT) were calculated using Equation (4)

$$MGRT_i = \frac{(100 - PR_i)\times{\gamma_{1,i}}^2\times{\beta_{1,i}}^{-1}\times\Gamma\left(\frac{2}{\beta_{1,i}}\right) + PR_i\times{\gamma_{2,i}}^2\times{\beta_{2,i}}^{-1}\times\Gamma\left(\frac{2}{\beta_{2,i}}\right)}{(100 - PR_i)\times{\gamma_{1,i}}^2\times{\beta_{1,i}}^{-1}\times\Gamma\left(\frac{1}{\beta_{1,i}}\right) + PR_i\times{\gamma_{2,i}}^2\times{\beta_{2,i}}^{-1}\times\Gamma\left(\frac{1}{\beta_{2,i}}\right)} \quad (4)$$

where $\Gamma(\ )$ is the gamma function.

Covariate selection and evaluation

Since the aim of the work was to assess the influence of age on gastric emptying, age was tested as a covariate after allowance for type of test meal as a known significant covariate. To facilitate the analysis, test meals used in the studies were divided into five categories: namely aqueous solution (water, sugar solutions, fruit juice), breast milk, formula (any variety, including nutritional shakes), semi-solid meals (pudding, rice cereal or oatmeal) and solid meals. The meal type was entered into the model as a binomial variable, either 0 (absent) or 1 (present). The effect of meal type was tested on different parameters of the model shown in Equation (1). Covariate selection was based on visual inspection of the η and covariate plots and AIC values.

After allowance for the effect of test meal type, the postnatal age and gestational age were each tested as covariates. Postmenstrual age was used for graphical purposes and was calculated as the mean or median gestational age of the subjects in the study plus the mean or median postnatal age in weeks. For preterm infants, their gestational age at birth (in weeks) was added to their postnatal age in weeks. For term infants, a standard full-term gestational age of 40 weeks was added to postnatal age in weeks. For adults, age in years was converted to weeks and 40 weeks was added. The method of gastric emptying determination was accounted for in the residual error model and thus was not included as a separate covariate. Having selected the best model it was subjected to visual predictive checks in PLT tools Version 4.0 (PLTsoft, San Francisco, CA).

Simulations based on the final model

The final model was coded in MATLAB Version 2010.2 (MathWorks, Natick, MA) and, using the associated parameter estimates, % remaining *versus* time plots was simulated for 1000 individuals covering the age range of 0.01 to 800 months for the five different meal types. The resulting MGRT values for the simulated individuals were calculated using Equation (4).

Results

Data characteristics

The initial literature search yielded a total of 7514 articles. Ultimately, 66 papers that reported the percentage of the test meal remaining at one or more time points were identified. The initial modelling was done using a dataset of 49 of these gastric emptying studies (representing 1457 individuals) covering an age range from preterm neonates at 28 weeks' gestation to adults. General characteristics of the studies are listed in Table 1 with more details in the supplementary material. Sampling times ranged from 20 to 300 min after meal ingestion, the number of time points per study ranged from 1 to 19, and the number of subjects per study ranged from 6 to 186. Sex demographics of subjects are shown in Figure 1. Of the 1457 subjects in the original data set, 637 were paediatric subjects (mostly neonates) in whom sex was not specified. Of the remaining subjects, 495 were paediatric and 325 were adults. Of the 495 paediatric subjects in whom sex was specified, 256 were male and 228 were female, and 403 were preterm neonates. Of the 325 adult subjects in whom sex was specified, 160 were male and 165 were female. The group of 165 adult women included those of both pre- and postmenopausal ages, but in most studies it was not possible to make this distinction. In addition, in one study

Table 1. Studies used to construct and (*) validate the final model. References for the studies can be found in the supplementary material for the online version of this article

Study no	Year	Study population	Age in months Mean (range)	Method	Meal	Feed category in analysis	Duration of sampling (min)	No of subjects	No of time points per subject
1	1980	Preterm neonates	(0–0.25)	D (PR)	10% dextrose solution	Aqueous	30	20	1
2	1980	Preterm neonates	0.5	D (PR)	Sugar solutions	Aqueous	30	16	1
3	2004	Preterm neonates	0.57 (0.20–1.2)	S (Tc)	Breast milk	Breast milk	120	10	2
4	1996	Preterm neonates	1.47 (0.5–2.77)	U/S	Breast milk	Breast milk	150	11	16
5	2000	Preterm neonates	1	D (PEG)	Breast milk/formula	Breast milk/formula	120	11	2
6	1997	Preterm neonates	0.77	U/S	Breast milk/formula	Breast milk/formula	120	32	9
7		Preterm neonates	0.73	D	Breast milk/formula	Breast milk/formula	180	31	2
8		Preterm neonates	0.87	D (PEG)	Breast milk/formula	Breast milk/formula	20	27	1
9	1994	Preterm neonates	0.36 (0.13–0.87)	U/S	Breast milk/formula	Breast milk/formula	200	14	17
10	2008	Preterm neonates	0.13	U/S	Breast milk/formula	Breast milk/formula	120	20	1
11*	1992	Preterm neonates	0.233	D	Breast milk/formula	Breast milk/formula	240	50	1
12	1999	Preterm neonates	0.9 (0.47–1.23)	U/S	Breast milk/formula	Breast milk/formula	120	21	6
13	1983	Preterm neonates	0.41 (0.20–1.1)	S (Tc)	Formula	Formula	30	16	1
14	1994	Preterm neonates	0.043	S (Tc)	Formula	Formula	120	20	16
15	1991	Preterm neonates	0.33	D (PR)	Formula	Formula	30	10	1
16	1978	Preterm/term neonates	0.011/0.04/0.071	D (PR)	5% dextrose solution	Aqueous	30	47	1
17	1975	Preterm/term neonates	0.033	D (PR)	10% glucose solution	Aqueous	30	12	1
18	2008	VLBW neonates	(0.2–1)	U/S	Breast milk	Breast milk	180	20	18
19	1996	Preterm neonates/infants	0.67 (0.2–2.23)	U/S	Breast milk	Breast milk	120	22	9
20	2007	Preterm neonates/infants	1.33	D	Formula	Formula	180	9	6
21	1982	Preterm neonates/infants	1.2 (0.23–2.1)	D (PEG)	Formula	Formula	120	10	6
22	1984	Preterm neonates/infants	1.5 (0.23–2.8)	D (PEG)	Formula	Formula	100	10	5
23	1985	Preterm neonates/infants	1.4 (0.47–2.3)	D (PEG)	Formula	Formula	100	11	5
24	1984	Term neonates	(0.1–0.17)	D (PR)	Sugar solutions	Aqueous	30	13	1
25	1980	Term neonates	0.30 (0.17–0.87)	D (PR)	10% dextrose solution	Aqueous	180	14	9
26	1992	Infants	9 (6–14)	D (PEG)	5% dextrose solution	Aqueous	80	10	5
27	1990	Infants	(0–12)	S (Tc)	Breast milk/formula	Breast milk/formula	2/3	90	2
28*	2011	Infants	1.57	U/S	Formula	Formula	3	21	1
29	1989	Infants	7.56 (1.68–19.0)	D (PEG)	Formula	Formula	3	12	4
30	2006	Infants	4.6	U/S	Formula	Formula	3	14	5
31	1993	Infants	4.3 (1–11)	S (Tc)	Formula	Formula	3	28	1
32	2007	Infants	3	S (Tc)	Formula	Formula	3	81	2
33	1988	Infants	5.7 (2–14)	S (Tc)	Rice cereal	Semi-solid	120	10	1
34	1988	Neonates/infants	1.2 (0.47–1.63)	U/S	Formula	Formula	180	6	12

(Continued)

Table 1. *Continued*

Study no	Year	Study population	Age in months Mean (range)	Method	Meal	Feed category in analysis	Duration of sampling (min)	No of subjects	No of time points per subject
35	1995	Preterm/term infants	0.8 (pre)/1.5 (term)	APT	Dioralyte/formula	Aqueous/formula	90	82	10
36	1983	Infants/children	35.7 (0.75–168)	D (PEG)	Water	Aqueous	60	30	4
37*	2012	Infants/children	18	S (Tc)	Breast milk/formula	Breast milk/formula	60	81	1
38*	2012	Infants/children	5 (infants), 84 (children)	U/S	'Milk'	Formula	20/120	44/11	4/13
39	1983	Infants/children	5.7 (1–23)/109 (24–174)	S (Tc)	'Milk formula'	Formula	60	49	1
40	2011	Children	110 (76.8–154)	MRI	Raspberry syrup soln	Aqueous	120	16	4
41	2012	Children	133 (98.4–150)	MRI	Raspberry syrup soln	Aqueous	60	14	2
42	1998	Children	84 (60–132)	S (Tc)	Pancakes	Solid	120	11	8
43	1987	Neon/inf/child/adolesc	10 (0.5–192)	S (Tc)	Apple juice	Aqueous	60	14	2
44	1984	Neon/inf/child/adolesc	1/8/19/42/120	S (Tc)	Breast milk/for/water	Breast milk/for/aq	120	44	2
45	1987	Neon/inf/child/adolesc	1.8/4.9/8.9/20.9/52.8/134	S (Tc)	Formula or pudding	Formula/semi-solid	60	186	1
46	1997	Children/adolescents	153.6	S (Tc)	Pancakes	Solid	120	17	11
47*	2011	Adults	840	S (Tc)	Sucrose solution	Aqueous	300	10	19
48*	2012	Adults	418	S (Tc)	Orange juice	Aqueous	60	7	1
49*	2011	Adults	598	S (Tc)	Formula/lemonade	Aqueous/formula	120	8	8
50	2011	Adults	744 (228–1008)	S (Tc)	Formula	Formula	240	14	4
51	1981	Adults	340 (240–432)	S (Tc)	Cow's milk	Formula	60	6	4
52	1989	Adults	504 (240–912)	S (Tc)	Liquid prot, fat, carb	Formula	60	88	8
53	2012	Adults	564	MRI	Liquid prot, fat, carb	Formula	60	6	2
54	2011	Adults	468	S (Tc)	Eggs/bread/milk	Solid	240	19	12
55	1989	Adults	336	S (Tc)	Tuna sandwich/milk	Solid	90	10	1
56	2000	Adults	372	S (Tc)	Egg/ham/bread/OJ	Solid	165	15	11
57	1985	Adults	320 (252–432)	S (Tc/In)	Chicken liver/water	Solid	120	13	12
58	2000	Adults	(204–960)	S (Tc)	Omelette	Solid	120	160	17
59*	2012	Adults	439	S (Tc)	Omelette	Solid	120	18	11
60	2004	Adults	(240–600)	S (In/Tc)	Water/omelette	Aqueous/solid	120	11	8
61*	2000	Adults	397.2	S (Tc)	Omelette	Solid	180	7	18
62*	1994	Adults	342 (240–564)	S (Tc)	Scrambled egg/bread	Solid	180	20	12
63	2011	Adults	565	S (Tc)	Egg white sandwich	Solid	240	23	3
64*	2000	Adults	355	S (Tc)	Egg sandwich	Solid	120	9	8
65*	2000	Adults	492	S (Tc)	Egg subst/bread/jam	Solid	240	123	3
66*	1992	Adults	444	S (Tc)	Egg sandwich	Solid	90	10	1

*Data used in model validation only.
neon, neonate; inf, infant; VLBW, very low birth weight; S, scintigraphy; Tc, ^{99}technetium; In, ^{111}indium; D, dilution method; PR, phenol red; PEG, polyethylene glycol; U/S, ultrasound; MRI, magnetic resonance imaging.

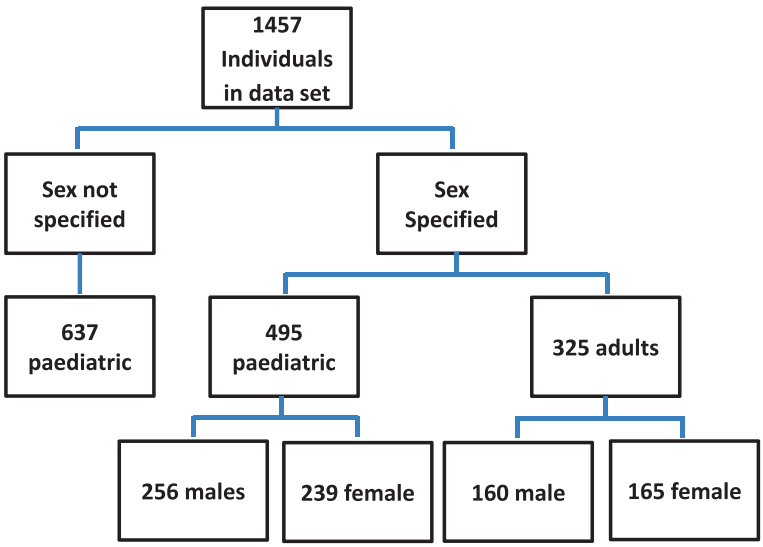

Figure 1. Age and sex of the subjects in the study data set

containing premenopausal females, all 44 subjects were studied in the first half of the menstrual cycle, which should have negated any potential hormonal effects on gastric emptying.

In the original dataset, the test meal was given orally in 22 studies, by nasogastric tube in 21 studies, by orogastric tube in four studies, and either orally or via tube in two studies. With regard to body position, the subjects were supine in 20 studies, prone in six, in the right lateral position in ten, sitting or standing in five, sitting or supine in one, prone or supine in one, and the subject position was not specified in six studies.

Final model selection

The objective functions for the three models that were tested are listed in Table 2. Based on these values and goodness of fit plots, the double Weibull function was selected as the final model. The results of the visual predictive check for the original data set are shown in Figure 2, and indicate that the majority of the observed data points fall within the 2.5th and 97.5th percentiles of the simulations with model parameters.

Covariates

Test meal type had a significant influence on the mean gastric residence time (as indicated by the objective function value). Addition of gestational or postnatal age in the final model did not change the objective function value, indicating they are not significant covariates.

The simulations with the final model indicated mean gastric residence times of 45 min for aqueous solutions, 57 min for breast milk, 64 min for formula, 87 min for semi-solid food

Table 2. Models evaluated and their objective function values (OFVs). The final model is indicated by a bold italic font

Model	Attributes	OFV
Exponential models	Combined error	2801.212
Exponential + lag time	Additive error	2696.632
Exponential + lag time	Combined error	2681.434
Double Weibull	Combined error	2176.032
Double Weibull (BASE MODEL)	Combined error + Accounting for number of individuals in study + Test type	2138.568
Covariate model	*BASE MODEL + Food types*	*1875.**252***
Covariate model	BASE MODEL + Food types + postnatal Age	1875.121
Covariate model	Food types + Gestational age	1875.211

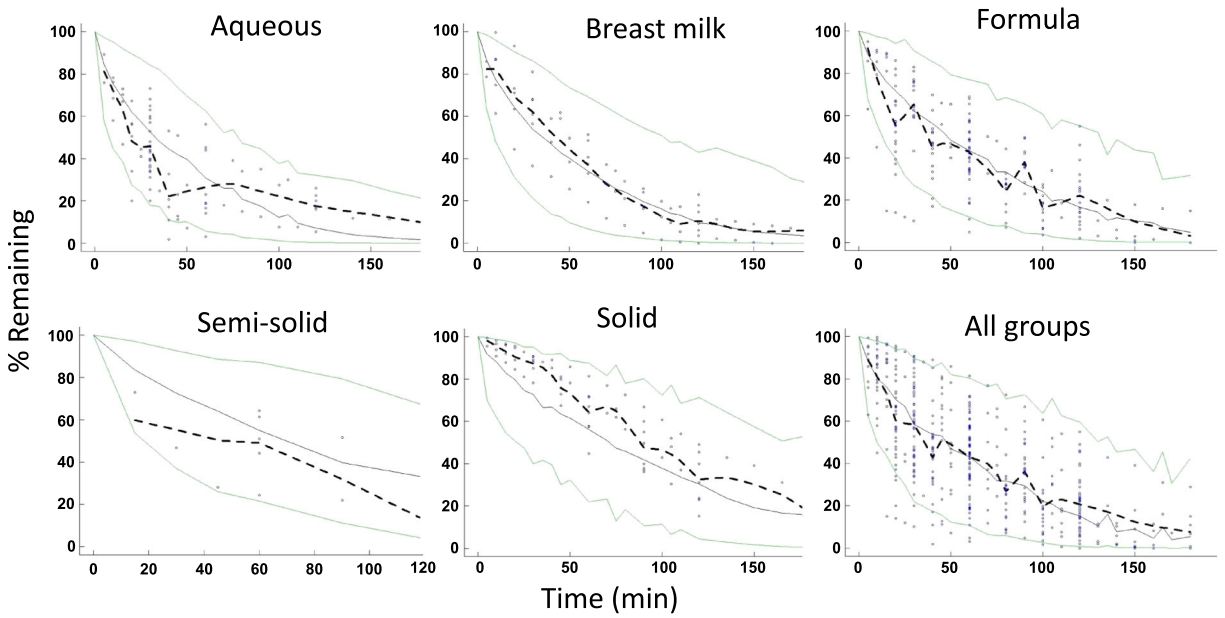

Figure 2. Visual predictive check plots. The green lines represent 2.5th and 97.5th percentiles of model-predicted data. The solid grey line represents the 50th percentile of model-predicted data. The dashed black line represents the median of the observed data

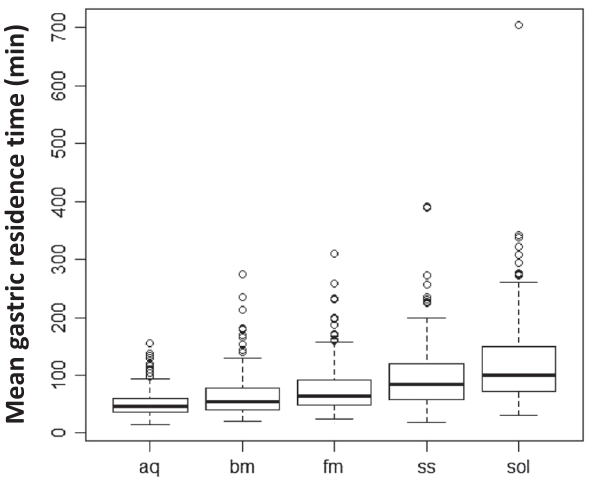

Figure 3. Box-whisker plots indicating a relationship between model-based simulated mean gastric residence time and meal type: aq, aqueous solution; bm, breast milk; fm, formula; ss, semi-solid meal; sol, solid meal

and 98 min for solid test meals (Figure 3). The lack of a relationship between MGRT and age irrespective of meal type is illustrated in Figure 4A, B.

Model evaluation

The final model parameter estimates and their precision are shown in Table 3, and the goodness of fit plots, including population and individual model predictions, individual weighted residuals against individual predictions and weighted residuals with time are shown in Figure 5. The residual plots indicate that no systematic error was detected in the final model. The result of the visual predictive check for the final model with respect to the independent validation dataset is shown in Figure 6. This shows that the majority of the data points in the independent data set also fall

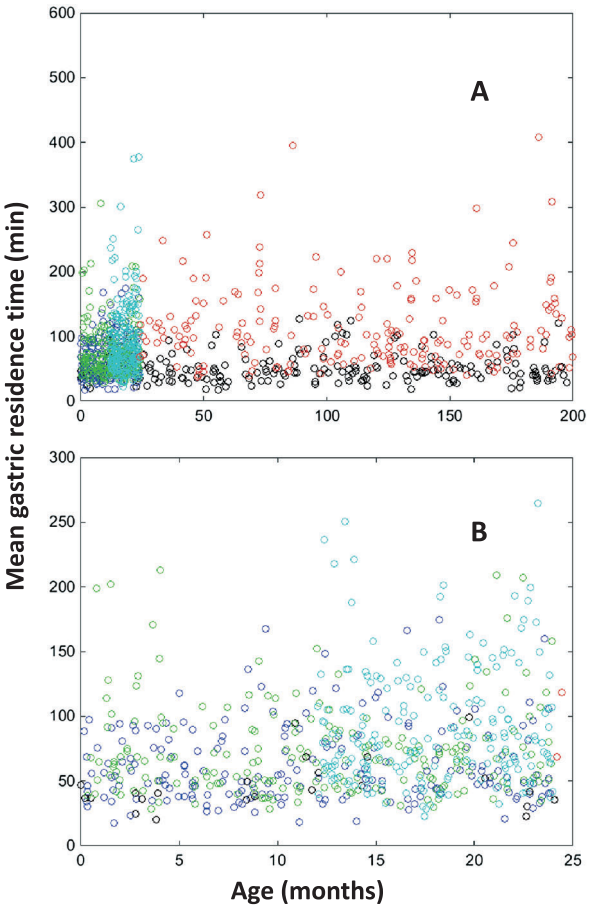

Figure 4. Model-based simulation of the relationship between postnatal age and mean gastric residence time, allowing for differences in the meal type. (A) whole 0–17 age range and (B) more detailed view for the 0–25 month age range. Open circles represent meal types: black, aqueous; blue, breast milk; green, formula milk; cyan, semi-solid; red, solid

within the 2.5th and 97.5th percentiles of the simulated data produced by the model. This indicates that the model predicts independent gastric emptying data well.

Discussion

This study has been the largest evaluation of covariates for gastric emptying involving paediatrics data. Our meta-analysis of 66 publications provided 'no evidence' for an effect of postnatal age or gestational age on the mean gastric emptying time, although a significant influence of meal

Table 3. Final population model parameters

Model parameter	Estimate (RSE)	Variability, ω^2 (RSE)
PR (%)	0.26 (17.7%)	114 (11.6%)
β_1	0.816 (6.1%)	38.6 (10.5%)
β_2	2.48 (11.3%)	14.1 (15.2%)
γ_1(min)	37.6 (21%)	58.7 (8.1%)
γ_2 (min)	63.7 (7.6%)	19.2 (28.1%)
$\boldsymbol{\theta}_{\mathbf{w}}$	11.1 (15.9%)	NA
$\boldsymbol{\theta}_{\text{Aqueous}}$	0.697 (25.3%)	NA
$\boldsymbol{\theta}_{\text{Breast milk}}$	0.959 (35.7%)	NA
$\boldsymbol{\theta}_{\text{Form}}$	1.15 (21.7%)	NA
$\boldsymbol{\theta}_{\text{Semi solid}}$	1.61 (37.5%)	NA
$\boldsymbol{\theta}_{\text{Solid}}$	1.99 (22.4%)	NA

The parameters γ_1 *and* γ_2 define the scatter and β_1 *and* β_2 define the shape of the Weibull distribution function; *PR* represents the remaining percentage of test meal in the stomach when emptying is temporarily halted (see Eq. (1)); θ_w is the weighted standard deviation (see Eq. (3)); θ_{Aqueous}, $\theta_{\text{Breast Milk}}$,$\theta_{\text{Form}}$, $\theta_{\text{Semi solid}}$ and θ_{Solid} are the coefficient estimates for the following food types as covariates, aqueous solution, breast milk, formula, semi-solid meals and solid meals, respectively. RES (%) is the relative standard error (%). NA, not applicable.

type was confirmed, with aqueous solutions emptying most rapidly and solid meals most slowly and with liquid meals falling in between. This is consistent with previous reports [2,37,38]. Strengths of our meta-analysis include the large number of subjects represented in the initial dataset (1457) that contained a significant number of preterm neonates of a variety of gestational ages, as well as a weighting method that gave a higher weight to scintigraphic measurement as the gold standard and to time points with data from individuals. In addition, the type of gastric emptying data used in this study (% remaining at various time points) is likely to be more reliable than the often-reported measure of gastric emptying half-life, which is subject to bias from the method of calculation and by extrapolation beyond the testing time.

There are also limitations to the analysis, given the diversity of study protocols. These include the relatively small number of subjects (24%) between the ages of 1 and 10 years. Further issues are the differences in body position across studies, the wide range of calorific, fat and protein contents and volumes of test meals and their method of administration, and the presence of some premenopausal women among the adult subjects in the database. Gastric emptying is reported to be faster in the prone and right lateral positions than when supine [39], although one study in neonates that specifically addressed the effect of body position

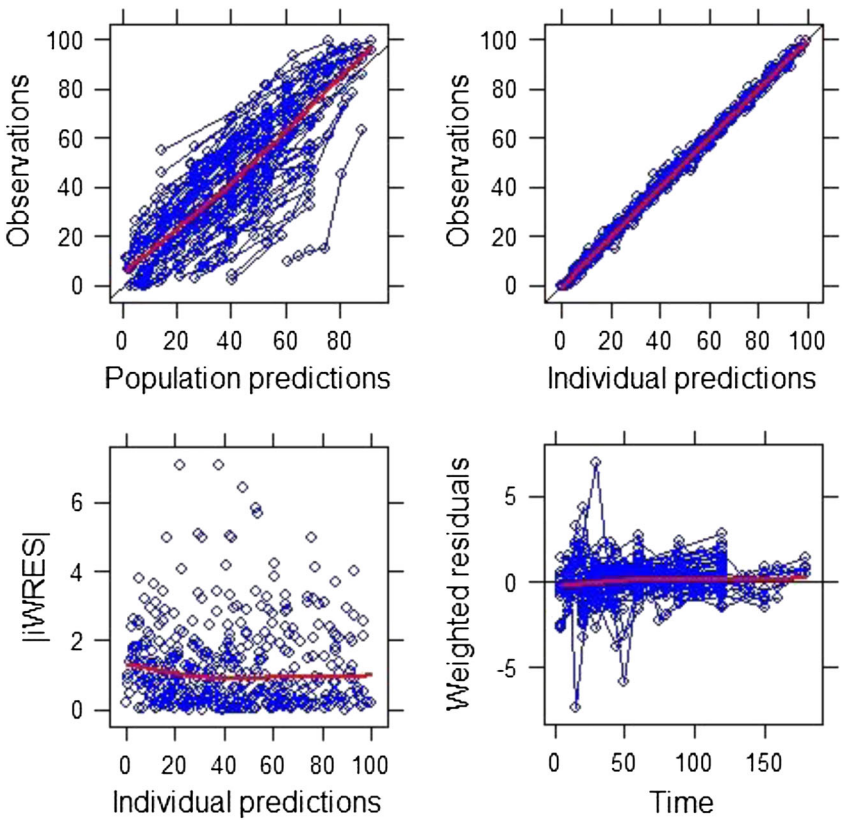

Figure 5. Goodness of fit plots showing population and individual predictions, individual weighted residuals against individual predictions and weighted residuals against time. Lines are the best fit to the data

showed no influence [40]. Ultimately body position was not included in the analysis because of the wide range of posture in the studies and the lack of convincing evidence of a strong effect. Significant variability in and missing information on the calorific, fat and protein contents and volumes of test meals and their method of administration across studies precluded any meaningful evaluation of these variables. Gastric emptying has been shown to be faster after a fatty compared with a protein based meal [41], and with greater feed calorific density and volume [41,42]. In the limited number of studies where information on feed volume was available a sub-analysis was performed but showed no significant correlation with measured gastric emptying (data not shown).

It should also be noted that age and test meal types were somewhat confounded in the analysis because semi-solid/solid meals were not tested in neonates such that the results only represent the age groups older than 2 months. However, aqueous and liquid meals were tested across all ages including around 150 adults spread over eight studies. A recent study in 700 children (which was published after the present analysis) has shown significantly faster gastric emptying associated with tube feeding relative to oral feeding [43]. As many newborns are tube fed this may have obscured an impact of age in this study. However, the same study also found no effect of age on gastric emptying when allowing for the feeding method.

With regard to the effects of differences in gender, although a slower gastric emptying rate has been noted in some studies in premenopausal females compared with postmenopausal females and males [44], likely due to the effects of oestrogens in the luteal phase of the menstrual cycle [45], most of the adult subjects in the dataset that was evaluated were men and postmenopausal women. Given the likely hormonal causes of slower gastric emptying in adult women of

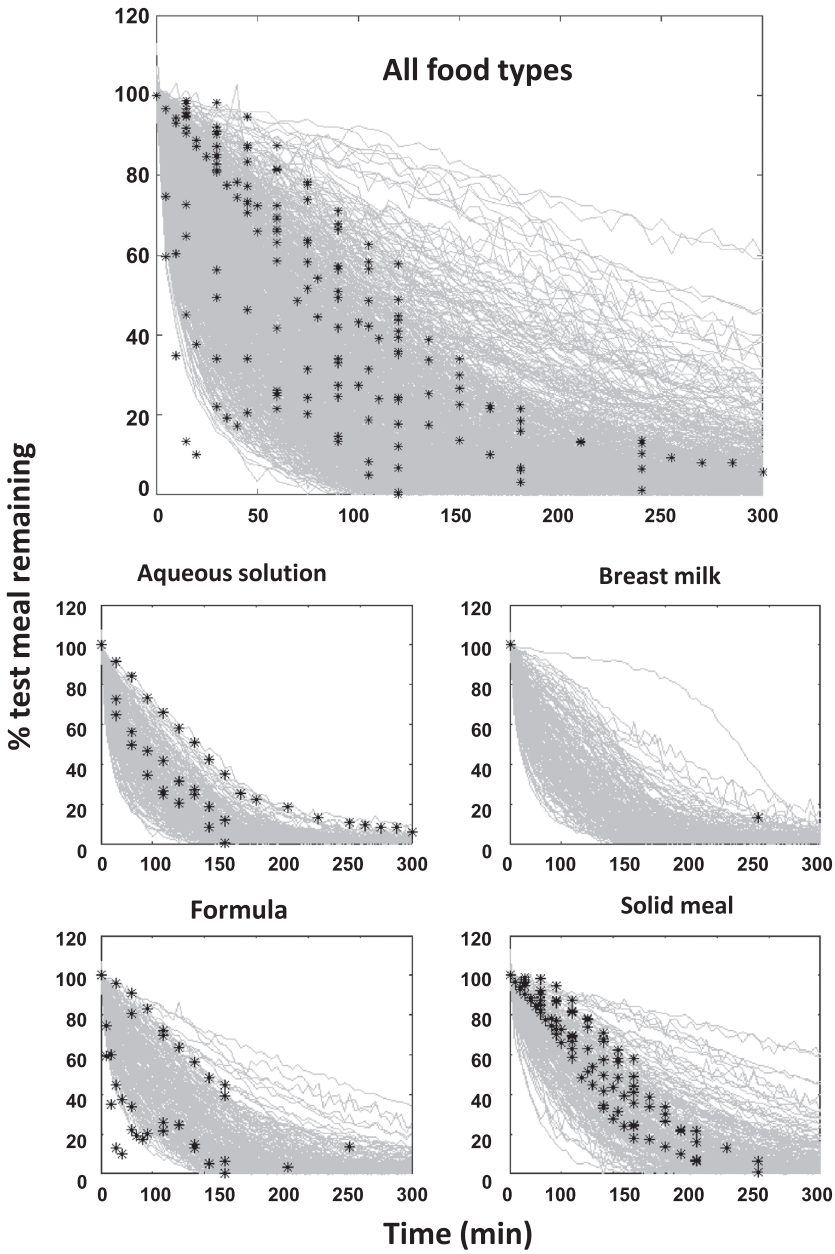

Figure 6. Visual predictive check (VPC) of the final model against the validation dataset in relation to meal type. Black stars are the observed data

reproductive age, the gender of the subject was assumed to have no effect on gastric emptying before puberty. Therefore, it was not accounted for in the overall analysis given that 1132 of the 1457 subjects (approximately 78%) in the dataset were paediatric. Since only 165 of the total 1457 subjects (577 adult subjects) were adult women it is unlikely that gastric emptying differences between males and females could have been shown from the data.

This study is part of a wider project to understand the underlying age related physiological changes that may affect oral drug absorption in the paediatric population with a view to the development of a paediatric *in silico* absorption

model. Such models will not only increase our understanding of the influence of specific GI system parameters on drug absorption but may also aid in the development of new oral formulations for this population.

Conclusion

Overall, the findings challenge the assertion that gastric emptying times are different in neonates, including premature neonates, compared with older children and adults, and reinforce the significance of food type in modulating gastric emptying time. Because of the limits of the available data, further prospective studies of gastric emptying times across a wide age range, using a liquid meal of consistent volume and nutritional content and using scintigraphy are warranted. However, for the purpose of developing a general model of paediatric drug absorption, the initial model will define gastric emptying time to be independent of age, although it will vary according to meal type in the fed state.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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