Age-mediated changes in the gastrointestinal tract

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Abstract

Physiological functions of the two extreme ends of the age spectrum, children (< 18 years old) and older adults (aged 65 years and over), differ from healthy young adults. This consequently affects the pharmacokinetic profiles of administered drugs, which, in turn, impacts upon clinical practice and drug therapy. The gastrointestinal milieu acts as a distinct and vital organ regulating the dissolution, absorption and metabolism of orally ingested drugs. Age-mediated alteration in the physiology and function of the gut can reshape the pharmacokinetics of certain drugs. However, our understanding on this topic is limited. This article references the gut physiology of healthy adults to capture the available evidence in the literature on the extent and nature of the changes in childhood and older age. The gut, as an organ, is examined with regards to the effect of age on luminal fluid, microbiota, transit and motility, and the intestinal mucosa. Whilst drastic developmental changes were observed in certain aspects of the gastrointestinal environment, the examination reveals significant gaps in our knowledge in the physiology and function of the developing or ageing gut. The revelation of the unknown paves the way towards a better characterization of the human gastrointestinal tract for optimized drug therapy in children and older adults.

Keywords:

Personalised medicine; paediatrics; geriatrics; ageing; absorption; gastrointestinal tract

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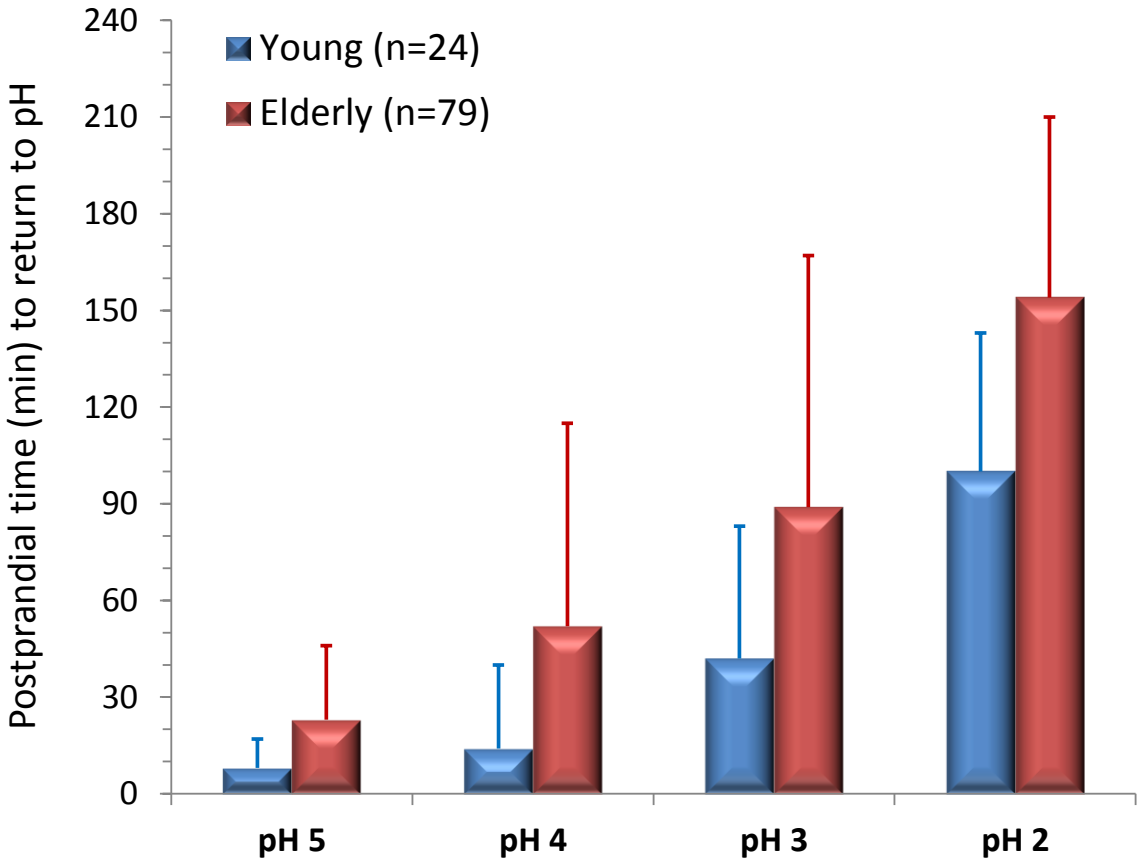

Figure 1. Postprandial time to return to pH 5, 4, 3 and 2 in elderly (65-83 years, n=79) and young (21-35 years, n=24) subjects. Figure plotted using data from (Russell et al., 1993).

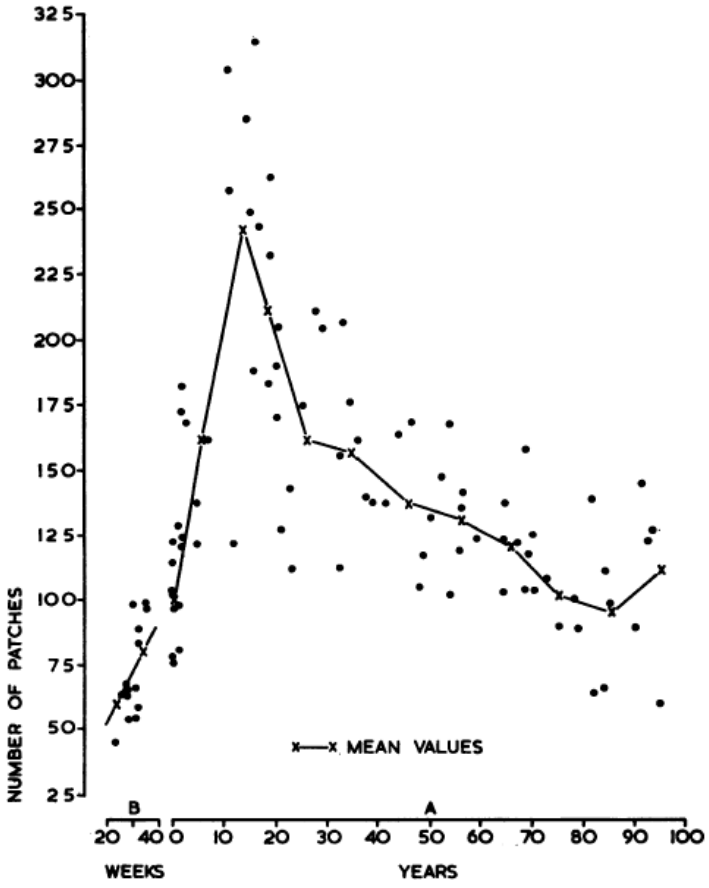

Figure 2. Effect of age on the number of Peyer's patches in human small intestine. B: before term (from 24 to 37 weeks gestation), A: after term (from birth to 95 years). Figure reproduced from (Cornes, 1965).

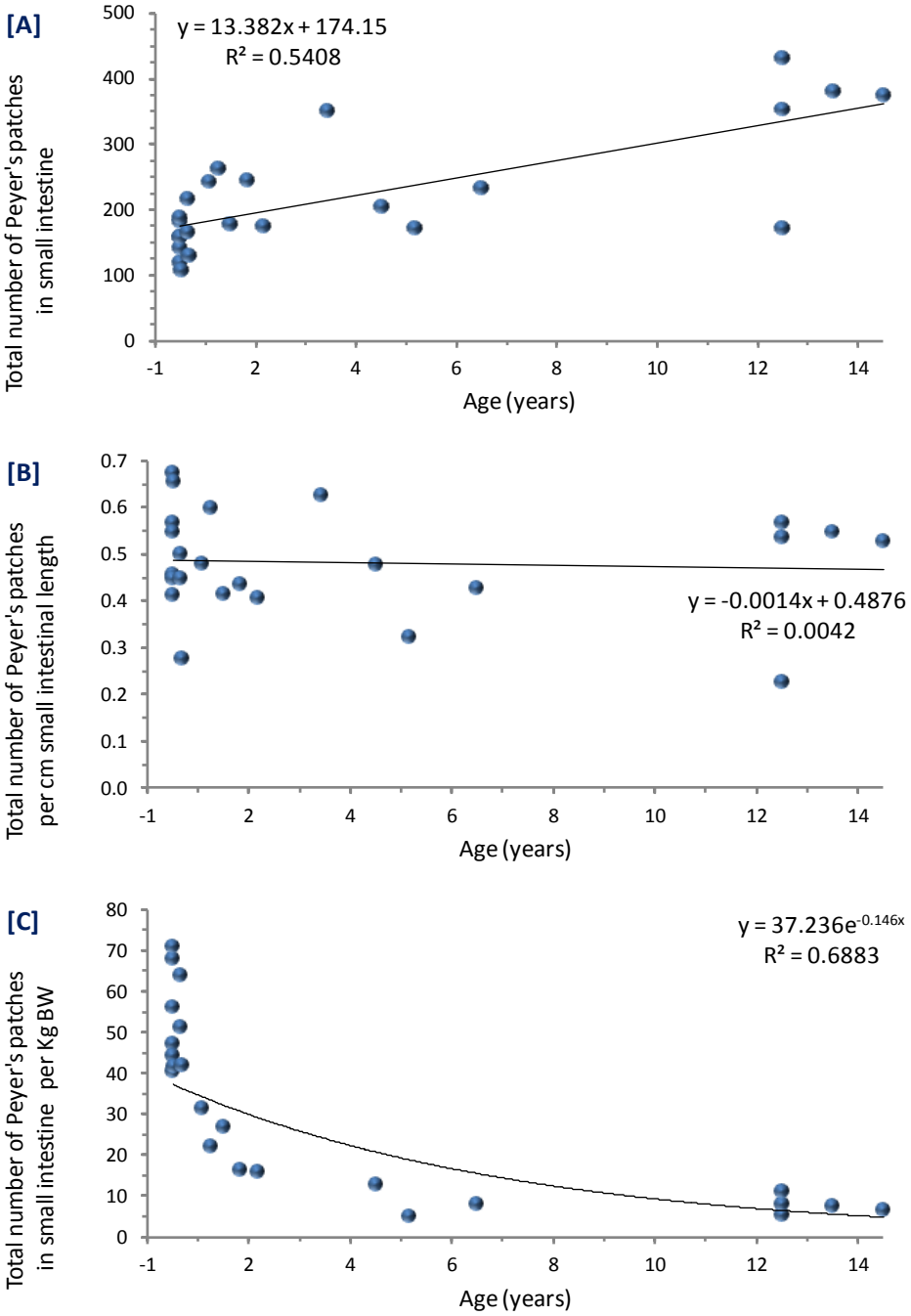

Figure 3. Effect of age on the number of Peyer's patches in human small intestine in subjects up to 14 years of age. Figure plotted using data from (Cornes, 1965).

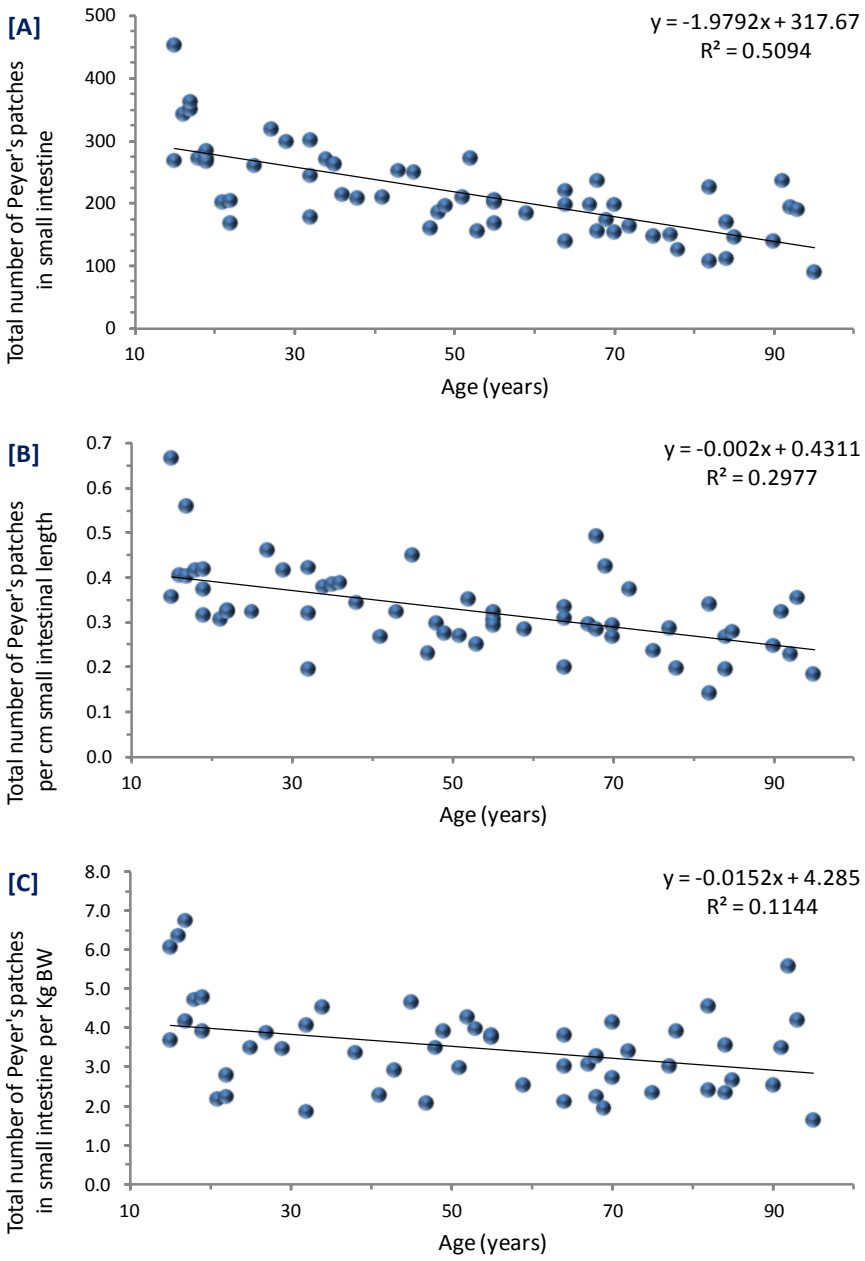

Figure 4. Effect of age on the number of Peyer's patches in human small intestine in subjects from 15 to 95 years of age. Figure plotted using data from (Cornes, 1965).

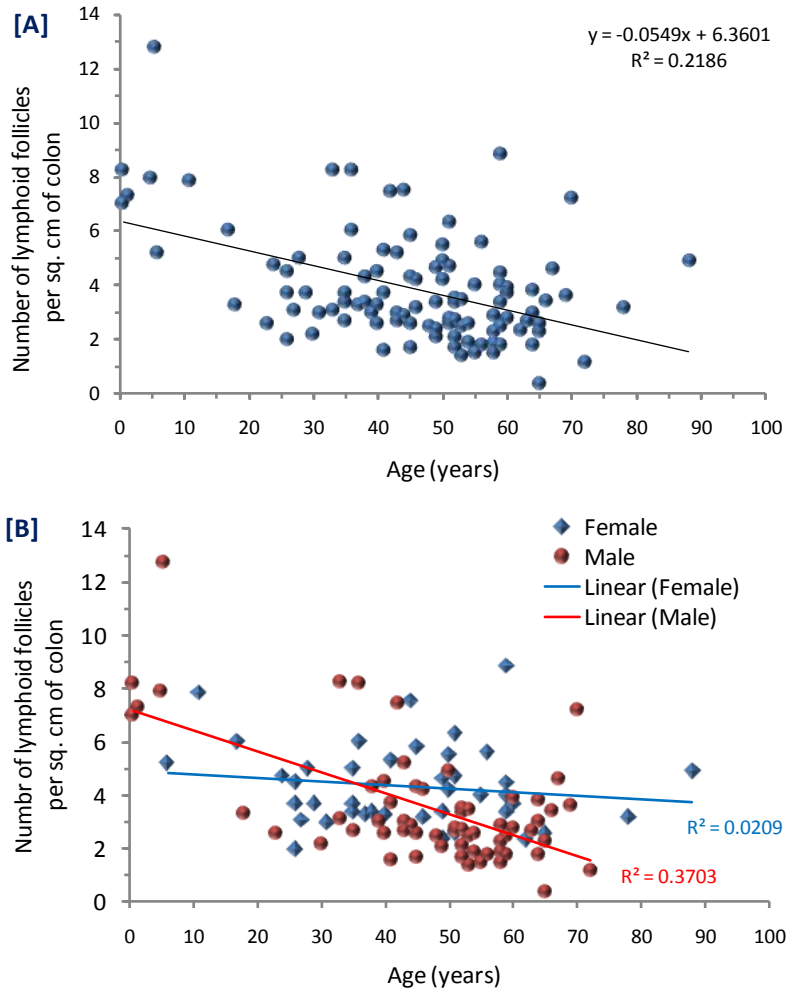

Figure 5. Effect of age on the number of lymphoid follicles per cm^2 of human colon. Figure drawn using data from (Dukes and Bussey, 1926).

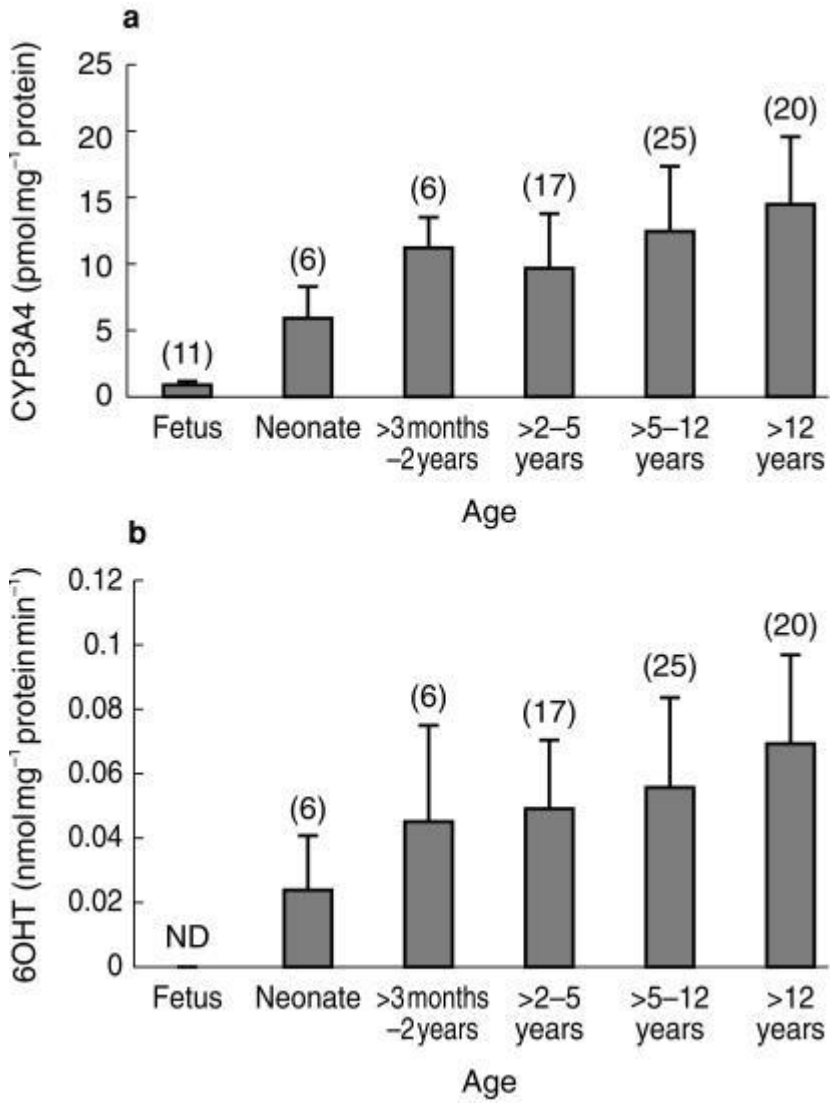

Figure 6. (a) Age related changes in the villi corrected expression of CYP3A4 in histologically normal duodenal sections. The numbers in each group are given in brackets and error bars are ± s.d. Statistical significance differences ($P < 0.05$) were achieved between foetus and all other groups and between neonate and children > 5 years. **(b)** Age related changes in villin corrected CYP3A4 activity measured by the rate of 6OHT formation in histologically normal duodenal sections. The numbers in each group are given in brackets and error bars are ± s.d. A statistically significant difference ($P < 0.05$) was observed only between neonates and children > 12 years. (Reproduced from (Johnson et al., 2001).

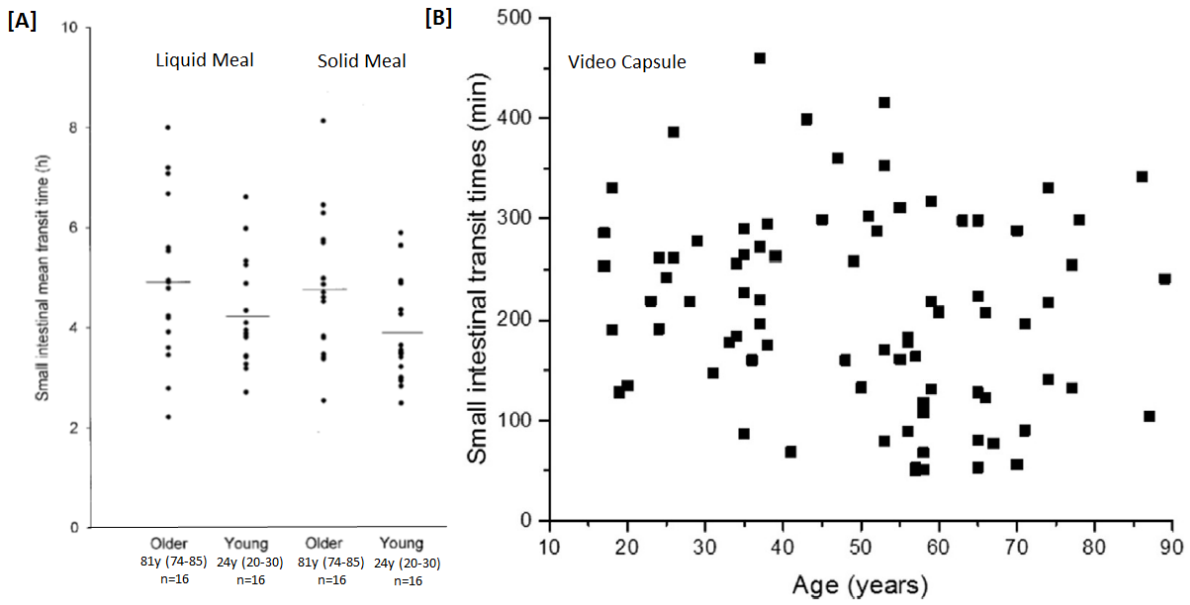

Figure 7. Effect of age on small intestinal transit time , figure adapted from [A] Madsen and Graff (2004) and [B] Fischer and Fadda (2016)

Table 1. Effects of ageing on the human gastrointestinal environment.

GI characteristics	Mean ± SD		
	Young	**Adult**	**Elderly**
pH	8-14 y (n=12)[1]	18-65 y (n=39)[2]	65-83 y (n=79)[3]
Stomach	1.6	1.5	1.1-1.6
Small intestine (SI)			
Duodenum	6.5	6.4	6.5
Jejunum	6.6	6.6	
Mid SI	7.0	7.0	
Distal SI	7.4	7.3	
Caecum	5.9	5.7	
Colon			
Ascending	5.6	5.6	
Transverse	5.5	5.7	
Descending	6.0	6.6	
Rectosigmoid	6.5	6.6	
Faeces	6.4	6.5	6.57[4]
Buffer Capacity (mmol/L/ΔpH)			
Stomach		14 (20-32 y)[5]	
Small intestine (SI)			
Duodenum		18-30 (20-32 y)[5]	
Jejunum		3.2 ± 1.3 [6]	
Ileum		6.4 [6]	
Caecum		-	
Colon			
Ascending		18.9 (20-30 y) [7]	
Transverse			
Descending			
Rectosigmoid			
Faeces			
Bile salts (mM), Duodemum			
Fasted		1.6-5.9[10-16]	
Fed	1.7 (under 2 days)[19]	~ 10[10-13, 17,18]	
	3.3 (2-7 days)[19]		
	8.5 (10 days to 7 mo)[19]		
Osmolality (mOsm.Kg^{-1})		226 ± 35 (18-25 y)ref	215 ± 37 (62-72 y)ref
Gut associated lymphoid tissue (GALT)			
SI (Peyer's patches) [8]	222 ± 91 (0-14 y)	273 ± 67 (15-38 y)	181 ± 43 (41-95 y)
Colon (follicles/cm^2) [9]	8.0 ± 2.3 (≤15 y)	4.0 ± 1.6 (16-40 y)	3.5 ± 1.6 (41-60 y) 3.1 ± 1.6 (61-88 y)

[1] Fallingborg et al 1990, [2] Fallingborg et al 1989, [3] Russell et al 1993, [4] Bouhnik et al 2007, [5] Kalantzi et al., 2006, [6] Fadda et al 2010, [7] Diakidou et al., 2009, [8] Crones 1965ab, [9] Dukes and Bussey 1926, [10] (Armand et al., 1996), [11] (Clarysse et al., 2009), [12](Persson et al., 2005), [13] (Dressman et al., 1998), [14] (Lindahl et al., 1997), [15] (de la Cruz Moreno et al., 2006), [16] (Deferme et al., 2003), [17] (Fausa, 1974), [18] (Kalantzi et al., 2006), [19] (Challacombe et al., 1975)

Table 2. Studies on the effect of aging on P-gp activity and expression in human.

Parameter tested	Cell type	Effects of aging	Reference
P-gp activity	B and T lymphocytes	↓	(Pilarski et al., 1995)
P-gp expression	T lymphocytes	↑	(Aggarwal et al., 1997)
P-gp activiety		↑	
ABCB1 expression		↑	
P-gp expression	Enterocytes	→	(Lown et al., 1997)
P-gp activity	B and T lymphocytes	→ or ↓	(Machado et al., 2003)
P-gp activity	Bone marrow stem cells	→ or ↑	(Calado et al., 2003)
P-gp activity	Natural killer cells	→	(Brenner and Klotz, 2004)
P-gp activity	Blood-brain barrier	↓	(Toornvliet et al., 2006)
ABCB1 expression	Liver	→	(Prasad et al., 2014)
P-gp activity	Blood-brain barrier	↓ in male, → in female	(van Assema et al., 2012)
P-gp activity	Intestine	→	(Larsen et al., 2007)
P-gp expression	Male lymphocytes	↑	(Vilas-Boas et al., 2011)
P-gp activity		→	

* Studies published prior to 2007 were adapted from (Mangoni, 2007). Increase (↑); decrease (↓); no change (→)

Table 3. Selected studies on the composition of the faecal microbiota in children, adults and the elderly*

Study population	Age	Total anaerobes	Bacteroides	Bifidobacterium	Enterobactria	Enterococci	Clostridia	Lactobacilli	Reference
Children	1 w		4.8 - 9.3	6.2 - 10.2	6.2 - 9.4	5.7 - 9.0	3.1 - 7.2	4.4 - 7.0	(Adlerberth and Wold, 2009)†
	5 w		6.0 - 10.1	4.3 - 11.3	6.1 - 9.6	4.5 - 9.6	3.0 - 8.1	5.0 - 9.1	(Adlerberth and Wold, 2009)†
	1 m		9.40 (5.74-10.36)	10.71 (6.84-11.56)			5.24 (2.70-9.57)	8.70 (7.92-10.73)	(Scheepers et al., 2015)
	16 m - 7 y	10.4 ± 0.2	9.9 ± 0.4	9.8 ± 0.3	8.0 ± 0.4	5.5 ± 0.5	7.2 ±0.8	6.6 ± 0.7	(Hopkins et al., 2002)
Adults	21 - 34 y	10.5 ± 0.1	10.0 ± 0.1	9.1 ± 0.2	5.9 ± 0.5	6.1 ± 0.7	6.6 ± 0.4	6.7 ± 0.6	(Hopkins et al., 2002)
	19 - 35 y		9.9 ± 0.1	9.5 ± 0.2	5.8 ± 0.6	6.5 ± 0.9	5.6 ± 1.0	6.3 ± 1.0	(Woodmansey et al., 2004)
	21 - 39 y	9.11	9.42	9.54					(Tiihonen et al., 2008)
Elderly	67 - 88 y	10.1 ± 0.2	9.6 ± 0.2	7.3 ± 1.0	6.7 ± 0.8	6.0 ± 0.8	6.9 ± 0.6	5.4 ± 1.0	(Hopkins et al., 2002)
	67 - 75 y		6.5 ± 2.1	8.1 ± 1.6	7.3 ± 0.4		5.3 ± 1,7	4.1 ± 1.8	(Woodmansey et al., 2004)
	> 62 y	10.3 ± 0.5		8.6 ± 1.0				6.0 ± 1.4	(Bartosch et al., 2005)
	69 ± 2 y	10.09 ± 0.07		8.5 ± 0.26	7.69 ± 0.21		3.25 ± 0.25		(Bouhnik et al., 2007)
	77 - 97 y		8.8	6.0	7.7	6.1	3.5	5.1	(Guigoz et al., 2002)
	68 - 84 y	9.29	9.59	9.59					(Tiihonen et al., 2008)

*Amounts are given as $\log_{10}$ number of bacteria/g fresh faecal weight, †Adapted from reference (Adlerberth and Wold, 2009), summarising studies on intestinal microbiota in children performed until 1990.

Conclusion and future perspectives

Age is an important determinant that impacts on the absorption and metabolism of drugs. It is apparent from this paper that many physiological and functional aspects of the human gut differ in children and older individuals from young adults. However, there are many knowledge gaps on age-related changes in the gut. The heterogeneity of both age groups further complicates the situation, as children do not develop at the same rate nor do the elderly age uniformly. Considering the rareness of healthy older patients, individual studies should be conducted on the geriatric population with co-morbidities and multiple medications, to consider the potential influence of concomitant diseases on the in-vivo fate of the drug in the gastrointestinal tract. Equally, further understanding on the chronological age-related changes (only healthy young and healthy older age-related) in the gut is important. In the case of the elderly, frailty should be a better indicator for the aged-gut compared to chronological age as the ageing status should be ideally defined by connecting the decline in physiological capacity and increased risk of vulnerability to disease.

Children and older patients are often underrepresented in clinical trials resulting in a lack of evidence based information on the effect of ageing on oral drug bioavailability. Although it is known that the function of GI tract is altered during developmental stages or with advanced age, the effects on pharmacokinetics and/or pharmacodynamics of the orally administered drug are often unclear. This data obtained from children and older subjects is essential as the prediction of clinical outcomes based on the gut physiological changes and/or extrapolation from healthy young adults may not be appropriate. The impact of prediction tools (e.g. physiologically-based pharmacokinetic /pharmacodynamics modelling and simulation) should be further explored to inform clinical trials in younger and older populations. Age related changes in barriers to drug delivery should be available to formulation scientists and adequately reflected in the design of personalized formulations to ensure the development of high quality, safe and effective drug therapies for use in young and older patients.

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