ORIGINAL ARTICLE

Application of adult reference intervals in children

Anne Bryde Alnor[1] · Pernille Just Vinholt[2]

Abstract

The aim of this study was to evaluate to which extend adult reference intervals (RIs) could be applied in children. A local paediatric population (aged 1 to < 20 years), based on first draw samples from general practitioners (GPs), was established. Children with samples taken at a hospital or > 3 samples from GPs were excluded. Analytes evaluated included haematological, liver and pancreatic function, kidney function, electrolytes, and metabolism parameters. Applicability of adult RIs in children aged 1–17 years was evaluated using individuals aged 18–19 years as reference groups for the adult RIs. The local population consisted of 31,024 children with 282,721 analyses in total. For each analyte, 17 age strata and two gender strata were established. Partitioning was not warranted in 51% of the male strata and in 69% of the female strata. Adult RIs could be applied in 42% for children aged 1–< 10 years, 57% for children aged 10–< 15 years, and 85% for children aged 15–<18 years.

Conclusion: for certain analytes, there is no need to partition between adult and paediatric RIs, but a need for age- and gender-specific RIs remains for several clinical laboratory tests.

What is Known:
- *Establishing paediatric reference intervals (RIs) is time consuming, costly, and not feasible for many laboratories. Transference of RIs established elsewhere often leads to misclassification of paediatric laboratory results.*
- *Adult RIs are often more easily established and validated.*

What is New:
- *Adult RIs can be applied to children as young as 2 years for some analytes. Conversely, for some analytes, adult RIs cannot be applied in children aged 1–17 years.*
- *Laboratory data can be applied in evaluating the need for partitioning in reference intervals.*

Keywords Paediatric · Reference interval · Adult · Applicability

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Abbreviations

Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMY	Amylase
AMYP	Amylase, pancreatic
AST	Aspartate transaminase
Bil, conj	Bilirubin, conjugated
BUN	Blood urea nitrogen
Ca	Calcium
CHOL	Cholesterol
CK	Creatine kinase
CLSI	Clinical and Laboratory Standards Institute
Cr	Creatinine
Erc	Erythrocytes

EVF	Erythrocyte volume fraction
F	Female
Fe	Iron
Glu	Glucose
GGT	γ-Glutamyl transferase
GP	General practitioner
HDL	High-density lipoprotein
Hgb	Haemoglobin
K	Potassium
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LH	Lillebaelt Hospital
Lkc	Leukocytes
M	Male
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
Mg	Magnesium
Na	Sodium
OUH	Odense University Hospital
P	Phosphate
PLT	Platelets
RI	Reference interval
SI	System of units
SD	Standard deviation
TGL	Triglyceride
TP	Total protein
UA	Uric acid

Introduction

Reliable paediatric reference intervals (RIs) are fundamental for the interpretation of laboratory results, and thus correct diagnosis and treatment of patients [1]. Establishing paediatric RIs can however be a precarious, costly, and time-consuming process, as sampling from healthy, representative children is recommended according to the Clinical and Laboratory Standards Institute (CLSI) guideline on establishing and verifying reference intervals [2]. Sampling from especially young children is furthermore technically difficult and associated with ethical considerations [3]. As an alternative, the CLSI notes that laboratories can transfer paediatric RIs established elsewhere onto their local population [2]. However, applicability of a transferred RI is questionable due to a substantial variation in methodology applied in the studies establishing paediatric RIs, which leads to vast differences in published paediatric RIs [4]. This is reflected by the fact that seemingly comparable RIs classify samples differently [4]. Generally, adult RIs are well documented [1], and the establishment of adult RIs tends to be more feasible than performing paediatric RIs. Therefore, the aim of this study was to apply a data mining approach to evaluate the extend of which partitioning between adult and paediatric RIs was warranted and thus whether adult RIs could be applied in a local paediatric population.

Methods

We defined a local paediatric population based on anonymous laboratory data of paediatric samples (age 1 to < 20 years) from general practitioners (GPs) analysed over a five-year period (September 2012–August 2017) at the Department of Clinical Biochemistry and Immunology, Lillebaelt Hospital (LH) and the Department of Clinical Biochemistry and Pharmacology, Odense University Hospital (OUH). Data were analysed and handled in agreement with the Danish Data Protection Agency and the regulations established by the National Committee on Health Research Ethics in Denmark. Both hospitals are situated in the region of Southern Denmark and have a catchment area of approx. 730,000 patients and analyse blood samples from local GPs. To ensure an overall healthy population, children who had samples requested from others than the local GP (i.e., a hospital department) in the corresponding period were excluded. Children with > 3 repeat measurements in the time period were also excluded and only the first sampling was included for further analysis. We evaluated children age 1 to 17 years, while individuals aged 18–19 years constituted the reference adult group. Each subgroup (1-year, gender subdivided stratum) was compared with this adult reference group to establish if the distribution allowed common reference intervals; i.e., if partitioning between adults and children was recommended or not. In accordance with the Clinical and Laboratory Standards Institute (CLSI) guideline on defining, establishing, and verifying RIs [2], ≥ 120 samples were required in each subgroup, and strata with < 120 samples were not evaluated.

We evaluated analytes for which adult RIs are well established by Rustad et al. [5] and Nordin et al. [6]. Analytes included haematological parameters, liver and pancreatic function tests, kidney function tests, electrolytes, and metabolism, see Table 1 for details. Haematological parameters in the local dataset were analysed using Sysmex XN-9000 (Sysmex, Kobe, Japan). The remainder was analysed with Cobas® 6000 (Roche Diagnostics, Switzerland) (LH until September 2015), Architect (Abbott Diagnostics, USA) (OUH until August 2017), and Cobas® 8000 (Roche Diagnostics, USA) (OUH August 2017 onwards, LH September 2015 onwards). Units are declared according to the International System of Units (SI), and SI units are used throughout this article.

Table 1 Analytes evaluated in the local paediatric population. Abbreviations, units, and reference intervals for the analytes evaluated. Frequency of analyte in the local paediatric population is shown

Abbreviation (unit)	Full name	Samples (n) in the LH/OUH population
Haematological parameters		
Hgb (mmol/L)	Haemoglobin	21,993
EVF (L/L)	Erythrocyte volume fraction	3015
Erc (10^{12}/L)	Erythrocytes	4034
MCV(fL)	Mean corpuscular Volume	7380
MCH (fmol)	Mean corpuscular haemoglobin	2738
MCHC (mmol/L)	Mean corpuscular haemoglobin concentration	6023
Lkc (10^9/L)	Leukocytes	23,243
PLT (10^9/L)	Platelets	17,870
Fe (μmol/L)	Iron	4848
Liver and pancreatic function tests		
Alb (g/L)	Albumin	2764
Bil, conj (μmol/L)	Bilirubin, conjugated	1130
AST (U/L)	Aspartate transaminase	3
ALP (U/L)	Alkaline phosphatase	20,333
GGT (U/L)	γ-Glutamyl transferase	11,594
ALT (U/L)	Alanine transaminase	22,246
LDH (U/L)	Lactate dehydrogenase	4358
TP (g/L)	Total protein	92
AMY (U/L)	Amylase	0
AMYP (U/L)	Amylase, pancreatic	7857
Kidney function and electrolytes		
BUN (mmol/L)	Blood urea nitrogen	8322
Cr (μmol/L)	Creatinine	22,905
CK (U/L)	Creatine kinase	1352
P (mmol/L)	Phosphate	890
UA (μmol/L)	Uric acid	3019
Na (mmol/L)	Sodium	20,782
K (mmol/L)	Potassium	20,904
Mg (mmol/L)	Magnesium	1145
Ca (mmol/L)	Calcium	8925
Metabolism		
CHOL (mmol/L)	Cholesterol	8650
HDL (mmol/L)	High-density lipoprotein	8601
LDL (mmol/L)	Low-density lipoprotein	8575
TGL (mmol/L)	Triglyceride	8461
Glu (mmol/L)	Glucose	1433

Statistics

The LH/OUH dataset was partitioned into 1-year age stratifications and subdivided into gender partitions. The dataset was transformed to a Gaussian distribution using the Box-Cox method and outliers were removed after stratification using Tukey's method [7]. Each stratified subgroup was compared with data from the adult group of the same gender (18–19 years) to evaluate whether partitioning was required or whether the same RI was appropriate. We used two partitioning criteria in accordance with Harris et al. [8]. First, we used Harris and Boyd's method [9], which evaluates difference in mean between two subgroups:

$$z = \frac{\overline{x}_1 - \overline{x}_2}{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^{\frac{1}{2}}}$$

In which, $\overline{x}_i$ is the mean, s_i is the standard deviation (SD), and n_i the sample size of the subgroup. The suggested critical value of z^* [8] was calculated as

$$z^* = 3\sqrt{\frac{n}{120}}$$

If $z < z^*$, partitioning was not recommended, and the adult RI could be accepted. Secondly, we applied the standard deviation (SD) criterion, in which the SDs of the subgroups were compared. If the ratio between the SDs exceeded 1.5, partitioning was warranted [8]. Thus, if neither the Harris and Boyd nor the SD criteria warranted partitioning, the adult RI was applicable for the specific paediatric subset. For calculation example, see supplementary data 1.

Frequencies are reported as numbers and percentages. Normally distributed data are presented as mean and standard deviation (SD), whilst median and interquartile range is used for non-normally distributed data. Data were analysed with Stata software package (Stata 15.1; StataCorp, College Station, TX, USA) and GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA).

Results

The final LH/OUH population consisted of 31,024 (Fig. 1), predominantly female (55%), children with 282,721 analyses in total (Table 1 and supplementary Table 1). For each analyte, 17 age strata and two gender strata were established. Data on amylase, aspartate transaminase, conjugated bilirubin, creatinine kinase, glucose, magnesium, phosphate, and total protein were excluded due to insufficient data (i.e., ≤ 120 individuals per subgroup). The most frequent analyses in the local population were leukocytes (lkc), creatinine (Cr), alanine transaminase (ALT), haemoglobin (hgb), potassium (K), sodium (Na), and alkaline phosphatase (ALP), which constituted 54% of the total analyses.

There were 850 (425 male and 425 female) possible paediatric partitions. Of these, 231 (54%) of the male (M) strata and 247 (58%) of the female (F) strata contained > 120 individuals (for details on number of samples for each analyte and partition, see supplementary Table 1). Table 2 shows where partitioning was warranted according to the criteria. Partitioning was not warranted in 118 (51%) of the male strata and in 171 (69%) of the female strata (for details on z, z^*3, and SD ratio values, see supplementary Table 2), i.e., adult RIs could overall be applied in 289 (60%) out of the 478 partitions evaluated. For ALP (M) and GGT (M), partitioning was necessary for all paediatric subgroups evaluated according to the z^*3 and the SD criteria. Conversely, EVF (F), Erc (F), MCH (F), Lkc (F), Plt (F), Fe (F), Alb (F), LDH (F), BUN, UA, Na (F), K, Ca, CHOL (M), HDL, and TGL did not warrant any

Fig. 1 Establishment of local dataset

Laboratory data (Sept.2012 – Aug. 2017):
98,835 individuals
- 2,708,166 blood analyses

Excluded → Samples taken at hospital in the corresponding period:
- 2,250,312 measurements

- 31,579 individuals
- 457,854 blood analyses

Excluded → Individuals with >3 repeat sampling:
- 104,141 measurements

- 31,042 individuals
- 353,713 blood analyses

Excluded → 2nd and 3rd sampling

Data included in the final dataset:
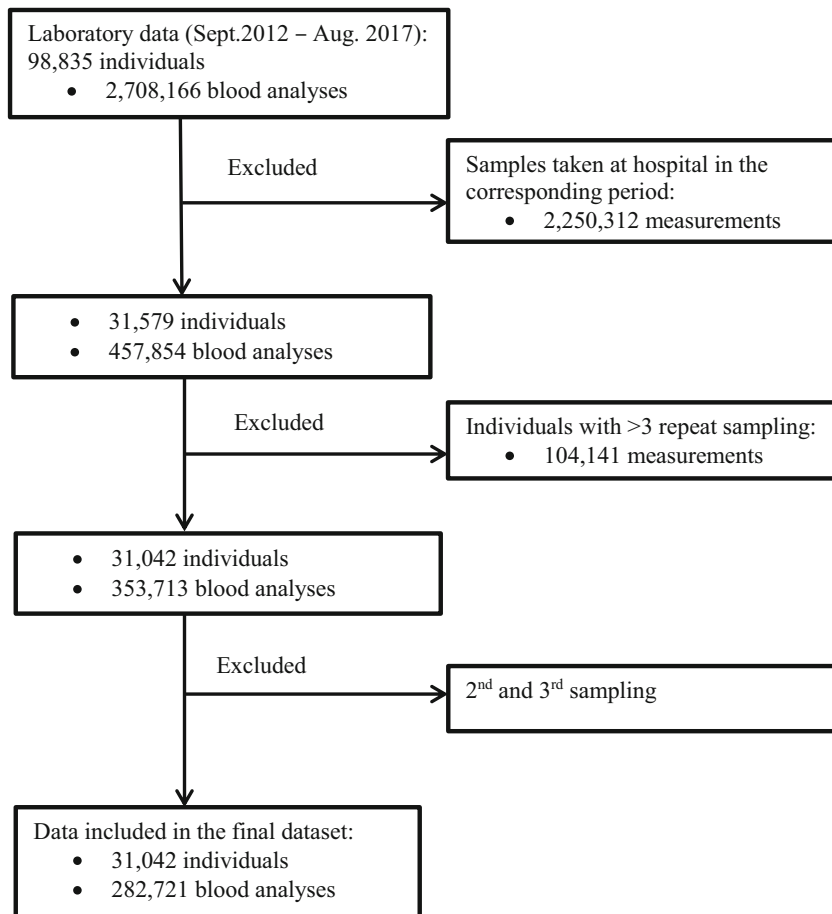- 31,042 individuals
- 282,721 blood analyses

Table 2 Evaluation of applicability of adult RIs for 1-year gender subdivided partitions. Dark boxes denote partitioning was not recommended, i.e., adult RI can be accepted. Light boxes denote partitioning was warranted. -Denotes fewer than 120 individuals in the respective age and gender stratum. *M*, male; *F*, female.

Analyte (unit)	Gender	Age (years)																
		17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1
Haematological parameters																		
Hgb	M																	
(mmol/L)	F																	
EVF	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(L/L)	F						-	-	-	-	-	-	-	-	-	-	-	-
Erc	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(10^12/L)	F							-	-	-	-	-	-	-	-	-	-	-
MCV	M											-	-	-	-	-	-	-
(fL)	F											-	-	-	-	-	-	-
MCH	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(fmol)	F		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MCHC	M										-	-	-	-	-	-	-	-
(mmol/L)	F											-	-	-	-	-	-	-
Lkc	M																	
(10^9/L)	F																	
PLT	M																	-
(10^9/L)	F																-	-
Fe	M					-	-	-	-	-	-	-	-	-	-	-	-	-
(μmol/L)	F							-	-	-	-	-	-	-	-	-	-	-
Liver and pancreatic function tests																		
Alb	M												-	-	-	-	-	-
(g/L)	F												-	-	-	-	-	-
ALP	M																-	-
(U/L)	F																-	-
GGT	M												-	-	-	-	-	-
(U/L)	F												-	-	-	-	-	-
ALT	M																-	-
(U/L)	F																-	-
LDH	M					-	-	-	-	-	-	-	-	-	-	-	-	-
(U/L)	F					-	-	-	-	-	-	-	-	-	-	-	-	-
AMYP	M											-	-	-	-	-	-	-
(U/L)	F											-	-	-	-	-	-	-
Kidney function and electrolytes																		
BUN	M												-	-	-	-	-	-
(mmol/L)	F														-	-	-	-
Cr	M																	
(μmol/L)	F															-	-	-
UA	M		-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
(μmol/L)	F						-	-	-	-	-	-	-	-	-	-	-	-
Na	M															-	-	-
(mmol/L)	F															-	-	-
K	M															-	-	-
(mmol/L)	F															-	-	-
Ca	M												-	-	-	-	-	-
(mmol/L)	F											-	-	-	-	-	-	-
Metabolism																		
CHOL	M							-	-	-	-	-	-	-	-	-	-	-
(mmol/L)	F							-	-	-	-	-	-	-	-	-	-	-
HDL	M							-	-	-	-	-	-	-	-	-	-	-
(mmol/L)	F							-	-	-	-	-	-	-	-	-	-	-
LDL	M							-	-	-	-	-	-	-	-	-	-	-
(mmol/L)	F							-	-	-	-	-	-	-	-	-	-	-
TGL	M							-	-	-	-	-	-	-	-	-	-	-
(mmol/L)	F							-	-	-	-	-	-	-	-	-	-	-

partitioning, indicating that adult RIs could be applied for all paediatric strata evaluated. The need for partitioning decreased with increasing age, but the age for which adult RIs could be applied varied according to analyte, see Table 2. Adult RIs could be applied in 65 (42%) out of 153 partitions for children aged 1–< 10 years evaluated. In comparison, in 107 (57%) of the 188 partitions for children aged 10–< 15 years, and 117 (85%) of the 137 partitions for children aged 15–< 18 years evaluated, adult RIs were regarded applicable. For two analytes (ALP (M) and GGT (M)), partitioning was also warranted in children aged 17 years. For 7 analytes (Hgb (F), MCHC (M), Fe (M), Alb (M), AMYP (M) CHOL (F), and LDL), there was an inconsistency between applicability of adult RIs and increasing age, as the adult RIs were applicable in the youngest and oldest age partitions evaluated but not in all of the age partitions in-between these.

Several analytes had fewer than 120 individuals per strata, and applicability of adult RIs could therefore not be evaluated. This was most pronounced for the younger children, as 34% of the strata for children aged 1–< 10 years had ≥ 120 individuals. In comparison, 74% of the strata from children aged 10–< 15 years and 91% of strata from children aged 15–< 18 years had ≥ 120 individuals). Table 3 summarized the age and gender partitions, for which adult reference intervals could be applied.

Discussion

The present study shows that for several analytes there is no need for partitioning between adults and children, meaning that in a majority of cases, adult RIs can be applied in a paediatric population. Overall, our data showed that in a local paediatric population adult RIs could be applied in 60% of cases, and there was a decreasing need for partitioning between adults and children with increasing age.

The need for partitioning was variable and depended on the specific analyte in question. Whilst some adult RIs were universally applicable for the age strata tested, others were only applicable for the oldest age groups. Our results are in line with the results from the CALIPER Pediatric Reference Interval Database [10, 11], which did not find partitioning warranted for Na, K, Ca, or TGL for children aged 1–< 19 years indicating an age- and gender-independent physiological function. Electrolytes, including Na, K, and Ca have low intra- and inter-individual biological variation [12], which supports the fact that no age- or gender-related partitioning is needed for these analytes. In contrast hereto, we found that adult RIs for Hgb could only be applied in boys aged > 16 years. Adult Hgb RIs could however be applied in girls as young as 5 years. The German KiGGS study [13] and the CALIPER study [14] found similar results, with greater variability in male Hgb levels than in females, supporting our findings.

Table 3 Paediatric age partitions in which the adult RIs could be applied. The table summarises the paediatric age and gender partitions for which the adult RIs were applicable according to the calculations. M, male; F: female; n/a: not applicable Supplementary data

Analyte (unit)	Gender	Adult RIs applicable in age groups (years)
Haematological parameters		
Hgb (mmol/L)	M	16–17
	F	5, 7–17
EVF (L/L)	M	n/a
	F	14–17
Erc (10^{12}/L)	M	n/a
	F	12–17
MCV (fL)	M	16–17
	F	14–17
MCH (fmol)	M	n/a
	F	17
MCHC (mmol/L)	M	9–13, 15–17
	F	13–17
Lkc (10^9/L)	M	3–17
	F	1–17
PLT (10^9/L)	M	14–17
	F	3–17
Fe (µmol/L)	M	14–15, 17
	F	12–17
Liver and pancreatic function tests		
Alb (g/L)	M	7, 10–12, 15–17
	F	6–17
ALP (U/L)	M	none
	F	17
GGT (U/L)	M	none
	F	17
ALT (U/L)	M	17
	F	15–17
LDH (U/L)	M	15–17
	F	14–17
AMYP (U/L)	M	10–11, 15–17
	F	15–17
Kidney function and electrolytes		
BUN (mmol/L)	M	6–17
	F	5–17
Cr (µmol/L)	M	17
	F	16–17
UA (µmol/L)	M	14, 17
	F	14–17
Na (mmol/L)	M	13–17
	F	4–17
K (mmol/L)	M	4–17
	F	4–17
Ca (mmol/L)	M	7–17
	F	8–17

Table 3 (continued)

Analyte (unit)	Gender	Adult RIs applicable in age groups (years)
Metabolism		
CHOL (mmol/L)	M	12–17
	F	12–13, 16–17
HDL (mmol/L)	M	12–17
	F	12–17
LDL (mmol/L)	M	12–14, 16–17
	F	13, 15–17
TGL (mmol/L)	M	12–17
	F	12–17

Childhood can be divided into separate developmental stages [15], with transitioning between these stages being highly individual, e.g., the onset of puberty [16]. Our finding of a decreasing need for partitioning with increasing age depict the physiological changes occurring with the transition from one stage to another. Interestingly, for some analytes, results stated that partitioning was warranted even for individuals aged 17 years, which generally surpasses the age when individuals are viewed as paediatric patients. Our results show that adult levels are reached at different ages, according to analyte and gender, which is important to bear in mind when diagnosing and treating children in general and teenagers in particular.

The Harris and Boyd criteria for partitioning used in this study is one of two methods recommended in the CLSI guideline [2]. The decision threshold of $z*3$ is based on a normal deviate testing of the significance of the difference between the means between two subgroups [8, 9]. Studies have suggested the criterion being relatively permissive of partitioning [17, 18]. The approach used in this study, where we combined the $z*3$ criterion with the SD1/SD2 $\leq$ 1.5 criterion, is therefore likely a conservative estimate of the applicability of adult RIs in children, and several "grey areas", in which the clinical implications of partitioning versus non-partitioning has to be assessed, may exist. That the data state that separate RIs are warranted for Na for boys aged 4–13 years is an example hereof, as it is highly improbable that there is an actual, clinically relevant difference in Na between boys aged 4–12 and boys aged > 13 years. The approach applied here, however, ensures that for the paediatric strata where no indication for partitioning was found, application of the adult RIs is sound. Furthermore, several studies on paediatric reference intervals do not specify the method used for age and gender partitioning, as an undefinable subjective evaluation has been used [4]. This can lead to misinterpretation of biochemical results, and the method outlined here can be of assistance in determining when partitioning is statistically reasonable.

The CLSI guideline [2] mentions the robust method by Horn and Pesce [19] for establishing RIs with < 120 reference individuals. With the robust method, there is no limit of required observations. However, identification of and direct sampling on healthy and representative children is still required, thereby favouring validation of transferred RIs with an indirect method. The indirect sampling method outlined here is both feasible and reliable for evaluating the local applicability of RIs. In children, RIs are often transferred from the literature, as this is a more feasible approach than the establishment of laboratory specific RIs. Importantly, we have recently shown that published paediatric RIs differ considerably in terms of methodology applied for establishing the RIs and subsequently also in classification of healthy paediatric samples. Thus, we found that 65% of a local paediatric haemoglobin results were shown to change classification from normal (within the RI limits) to abnormal (above or below the RI limits) [4]. Several large and well-documented studies on adult RIs exist [5, 6, 10, 20], and applying adult RIs in paediatric populations could be advantageous where physiological differences are insignificant, because adherence to the recommendations regarding the establishment of a RI is more feasible in adults than in children.

There are some limitations to our approach; even though children with > 3 repeat samples and hospital contacts were excluded from the local population, it does not guarantee a completely healthy population, as an indication for biochemical analysis has been present for each child included. As the study was conducted on anonymous laboratory data, information regarding life style was not available. However, we believe that the approach outlined here ensures that critically ill children and children with prolonged illness have been excluded. Furthermore, the size of the dataset, which consists of > 31,000 children, ensures that few abnormal (i.e., diseased) values will have little influence and would be expected to be removed as outliers. As the inclusion of diseased children would in worst case tend to skew data and therefore expectedly lead to partition recommendation, it does not limit the results where partition is not recommended. The approach outlined here is thus feasible for evaluating transference of adult RIs onto paediatric populations. Another limitation is that the adult population in this study constituted 18–19 year olds. Individuals aged > 18 years are often regarded as adults, particularly in terms of RIs, but they may not be representative of an entire adult population, which has to be taken into account. Our data show the importance of partitioning based on physiology, which is reflected in the data and thus the need for age- and gender-specific partitioning. Generally, partitioning is only relevant in cases where it is of clinical relevance and thus illustrates a clinically relevant difference. In this study, data for MCHC (M), Fe (M), Alb (M), CHOL (F), and LDL suggest varying partitioning between adult and paediatric values according to age. It is however unlikely that this depicts a true, clinically significant difference. The method used in this study is permissive of separate

partitions. Albeit this being a potential pitfall, the method ensures that in cases where no partitioning was found warranted, the RI can safely be applied. Altogether, our data underline the importance of combining clinical evaluation with biochemical results for correct diagnosis and management of the individual patient, which has also been stated by Harris and Boyd [8, 9, 17], Lahti et al. [18, 21, 22] and several others working with reference intervals [3, 23–25]. In children, it is vital to have RIs partitioned based on physiology, as emphasised in the CLSI guideline [2]. In prospective studies using a direct sampling approach, physiological considerations are important to ensure sufficient number of samples to establish the RI partitions needed. In that aspect, the indirect approach outlined here is more robust, as physiology is reflected in the biochemical results. Therefore, evaluating the need for partitioning is based on physiology in the indirect method. A final limitation of our study is that it only covers the most commonly applied analytes. With the data mining approach outlined here, it is possible to access large datasets that enable validation of complex analytes with statistical validity. There is a need for larger studies to validate our findings and evaluate data for rare analyses.

We do not advocate for the use of the adult RIs established by Rustad et al. [5] and Nordin et al. [6] in paediatric populations as we did not test whether there reference intervals were appropriate for the adult population. Rather, we wanted to contribute to a re-evaluation of the conventionally used partitioning between children and adults, and therefore the need for establishing specific paediatric reference intervals with the well-known problems connected hereto.

In conclusion, for several analytes, there is no need to partition between adult and paediatric RIs, but a need for age- and gender-specific RIs remains for several clinical laboratory tests and careful evaluation of the clinical implications of specific reference intervals must be always be considered. The use of laboratory data is however a feasible and reliable approach to evaluate the applicability of reference intervals.

Compliance with ethical standards

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