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Creatinine-based formulae poorly match in the classification of hypofiltration or hyperfiltration in a general population of adolescents. A retrospective analysis of a cross-sectional study

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Abstract

Pediatric formulae to estimate glomerular filtration rate (eGFR) give a broad range of values. Their consistency in assigning the subjects as hypofiltrating or hyperfiltrating is unknown. In 1,993 apparently healthy adolescents (53.4% females) aged 14-to-17 years, we investigated the concordance of six creatinine-based formulae in the classification of the subjects into $\leq 5^{\text{th}}$ or $\geq 95^{\text{th}}$ percentile of eGFR; and the between-groups difference in the prevalence of cardiometabolic risk factors. Mean eGFR varied between 77-to-121 mL/min/1.73 m². Arbitrary setting of hypofiltration or hyperfiltration to 5% returned 46 males and 53 females. At least one formula classified 89 males and 99 females as hypofiltrating, and 105 males and 114 females as hyperfiltrating. All six formulae concordantly classified 15 males and 17 females as hypofiltrating; and 9 and 14, respectively, as hyperfiltrating. Pairwise, formulae consistently classified hypofiltration in 42%-to-87% subjects, hyperfiltration in 28%-94%. According to two out of six formulae, hyperfiltration associated with increased prevalence of obesity and obesity-associated comorbidities. Hypofiltrating subjects did not manifest chronic kidney disease-associated comorbidities. Further studies in different populations of healthy adolescents are needed before it is possible to conclude on which creatinine-based formula is appropriate for the classification of hypofiltration and hyperfiltration in non-clinical cohorts.

Introduction

The worldwide increasing prevalence of hypertension and obesity in juveniles may predispose to a rise in the manifestation of chronic kidney disease. Obesity-associated hyperfiltration is an antecedent of future chronic kidney disease^{1,2}. Adolescent hypertension doubles the risk of end-stage renal disease regardless of the severity of hypertension and overweight³. This urges the need for effective assessment of renal function in the general population of adolescents.

Serum creatinine-based estimated glomerular filtration rate (eGFR) is a widely used marker of renal function both in clinics, and epidemiological studies. Despite that it is imperfect, it is generally employed since more accurate approaches for direct GFR assessment - renal clearance and plasma clearance methods – can only be performed in specialized centers^{4,5}. Urinary measurement of creatinine clearance requires the active cooperation of the subject in the accurate collection of urine over the period of 24 hours. The more accurate cystatin C-based estimation of GFR⁵⁻⁷ is several times more expensive than the creatinine-based one. Thus, neither of these approaches is feasible in general practice or epidemiological studies. Formulae estimating GFR in adults, such as the MDRD or CKD-EPI equations^{8,9} are not applicable to children and adolescents¹⁰⁻¹².

Derivation of universal pediatric equations faces several problems, such as sex differences in the growth spurt and in muscle mass gain^{4,5,13,14}. Currently, several equations derived from pediatric patients with renal disease or a general population of healthy subjects are available but none of them ideally reflects measured GFR^{4,5}. Studies in the general population of children and adolescents, and pediatric patients with type 1 diabetes (T1D) comprehensively documented the disparities and errors between measured and estimated GFR and showed that different equations to estimate GFR return values in a broad range¹³⁻¹⁶. However, it remains unclear whether different formulae consistently categorize adolescents into the lower and upper tail of eGFR distribution.

Concordance in assigning is of clinical importance as a manifestation of low or high eGFR requires further diagnostic steps. To these points, we compared serum creatinine-based eGFR values obtained by six different equations in a large cohort of apparently healthy adolescents. We anticipated that the highest correlation across eGFR ranges, as well as the highest consistency in assigning subjects into the tails of eGFR distribution, will be between pairs of equations derived from the same population. We also studied whether individuals with eGFR $\leq 5^{\text{th}}$ percentile present morbidities that are commonly associated with decreased renal function, and whether those displaying eGFR $\geq 95^{\text{th}}$ percentile present obesity and obesity-associated risk markers.

Results

Males (n = 929) and females (n = 1,064) were of similar age (16.1 ± 0.8 years and 16.2 ± 0.8 years, respectively). Mean serum creatinine concentration was 74.8 ± 13.2 $\mu\text{mol/L}$ in males and 60.9 ± 7.6 $\mu\text{mol/L}$ in females. Forty-three (4.5%) males and 13 (1.2%) females presented serum creatinine levels above their age-specific upper reference limit defined by Pottel et al. ¹⁷.

Glomerular filtration rate estimated via different formulae. Descriptive characteristics of data on eGFR obtained by each formula are given in Table 1. In both sexes, the LM equation yielded the lowest mean eGFR values and also the lowest cut-offs for the 5th and 95th percentile. The highest values were obtained using Léger's formula. The difference between means returned by Léger's vs. Lund- Malmö (LM) formula reached about 41 mL/min/1.73 m² in males and 45 mL/min/1.73 m² in females. At the 5th percentile, it corresponded to about 29 mL/min/1.73 m² and 33 mL/min/1.73 m², respectively; at the 95th to about 56 mL/min/1.73 m² in males and 62 mL/min/1.73 m² in females.

Employing the LM equation, 43% of males presented eGFR <75 mL/min/1.73 m²; Schwarz-Lyon formula assigned to this category about 11% of males; with the other four equations, the prevalence was <3% (Table 1). In females, the prevalence of eGFR <75 mL/min/1.73 m² reached about 47%, 8%, and 0%-to-1%, respectively. Using Léger's and the full-age spectrum with Q-height extension (FAS-QH) formulae, the prevalence of eGFR ≥ 135 mL/min/1.73 m² reached about 19% and 15%, respectively in males, and 22% and 6%, in females. The remaining four formulae returned prevalence between 0.1%-to-2%, in both sexes.

Mean eGFR calculated using the Schwarz-Lyon (Sch-L) formula did not differ between the sexes. Léger's, Lund- Malmö formula with lean body mass extension (LM-LBM), and the full-age spectrum with Q-age extension (FAS-QA) equation, gave higher mean eGFR in females compared with males; the opposite was observed using the LM and FAS-QH equations (Table 1).

For a better understanding of the differences, chart-flows of serum creatinine concentration and eGFR values returned by six formulae across 1st to 99th percentile were plotted (Figure 1a and 1b). Among two formulae derived from different cohorts of children with chronic kidney disease, in both sexes, Léger's equation returned higher eGFR values compared with the Sch-L equation. As for formulae derived from the same populations, in both sexes, the LM-LBM equation returned higher eGFR values compared with the LM formula. From eGFR >82 mL/min/1.73 m² in males and about 104 mL/min/1.73 m² in females, FAS-QH gave higher eGFR values compared with FAS-QA, particularly in males (Fig. 1a and 1b).

In males, LM-LBM, FAS-QA, and FAS-QH equations returned similar eGFR values at the 1st percentile (Fig. 1a). Thereafter, the slope of the LM-LBM equation flattened, and from the 95th percentile onward (about 113 mL/min/1.73 m²), LM-LBM eGFR values copied those returned by the Sch-L equation. Up to the 5th percentile, both FAS formulae gave almost identical eGFR values. While the slope of the FAS-QA equation showed minor variations across the percentiles, that of the FAS-QH equation rose more steeply, matching the values returned by Léger's formula at 95th and 99th percentile (i.e., ≥ 155 mL/min/1.73 m²).

In females, eGFR lines of both FAS and the LM-LBM formulae started to deviate above the 50th percentile, corresponding to eGFR of 102-106 mL/min/1.73 m². Thereafter, the slope of the LM-LBM formula flattened, reaching at 99th percentile value similar to that returned by the Sch-L equation; while that of FAS-QH equation rose more rapidly than that of FAS-QA but in contrast to males it did not reach values returned by Léger's equation at 99th percentile (Fig. 1b).

In both sexes, coefficients of determination between LM and Sch-L, LM and FAS-QA, and LM-LBM and Léger's equations were > 0.9 (Table 2). Schwartz-Lyon showed a good correlation with LM-LBM or FAS-QA formulae both in males and females, while in females it reached a value > 0.8 also vs. FAS-QH formula. In both sexes, equations derived from the same population, i.e., FAS-QH vs. FAS-QA or LM vs. LM-LBM, showed poor association (Table 2).

Consistency of six formulae in the classification of subjects as hypofiltrating. Arbitrary setting of the prevalence to 5% returned 46 males and 53 females. At least one formula classified 89 males as hypofiltrating. Six formulae matched in the classification of 15 males (17% out of 89); 10 (11%) subjects were concordantly classified by any 5 as well as by any 4 formulae out of 6; 3 equations consistently identified 12 males (13%), 2 formulae achieved concordance in 19 males (21%), and in 23 males (26%) only one out of 6 formulae indicated hypofiltration.

As for the concordance of classification between the pairs of equations, the Sch-L vs. LM-LBM, and LM vs. FAS-QA showed the highest (80%, both), and two FAS equations the lowest (43%) concordance in sorting males to the lower tail of eGFR distribution (Table 3). E.g., of 46 males classified as hypofiltrating by Sch-L formula, the LM-LBM equation classified as hypofiltrating 37; while 43% concordance observed for FAS formulae means that the second formula denotes as hypofiltrating 20 out of 46 subjects in the lower tail of the distribution of the first formula.

Among females, 99 were classified as presenting hypofiltration by at least one formula. All 6, and any 5, 4, 3, and 2 formulae concordantly classified 17, 12, 12, 11, and 26 females, respectively; corresponding to 17%, 12%, 12%, 11%, and 26% out of 99 subjects. One formula indicated hypofiltration in 21 females (21%).

In females, FAS-QA vs. LM; LM-LBM vs. Léger's, and LM vs. Sch-L equations yielded the highest (87%-to-81%) matches in the classification of hypofiltration; while the poorest concordance (42%) was between the FAS formulae (Table 3). E.g., while FAS-QA and LM formulae indicating 87% matching concordantly assigned as hypofiltrating 46 of 53 females, in the case of two FAS formulae it was 22 out of 53.

Consistency of six formulae in the classification of subjects as hyperfiltrating One hundred and five males were classified as hyperfiltrating by at least one formula. Six formulae matched in the classification of 9 males (about 9% out of 105); 8 (8%) subjects were concordantly classified by any 5, 12 (11%) by any 4 formulae out of 6; 3 equations consistently identified 18 males (17%), 2 formulae achieved concordance in 22 males (21%), and in 36 males (34%) only one out of 6 formulae indicated hyperfiltration. Léger's and LM-LBM, and SchL and LM formulae reached a consistency of 85% and 83%, respectively, in assigning males as hyperfiltrating (Table 3). The poorest concordance (28%) was revealed between the two FAS formulae.

Among females, 114 were classified as presenting hyperfiltration by at least one formula. All 6, and any 5, 4, 3, and 2 formulae concordantly classified 14, 10, 12, 13, and 33 females, respectively; corresponding to 12%, 9%, 11%, 11%, and 29% out of 114 subjects. One formula indicated hyperfiltration in 32 females (28%). As in males, Léger's and LM-LBM formulae showed the highest matching (94%) in the classification of hyperfiltration, followed by LM with FAS-QA (79%) (Table 3). The poorest agreement (40%) was observed between LM and LBM, as well as between LM and Léger's equations.

Comparison of mean age, height, and the prevalence of cardiometabolic risk markers among adolescents with eGFR $\leq 5^{\text{th}}$ versus $\geq 95^{\text{th}}$ percentile by various pediatric GFR estimating equations. Using all but FAS equations, males classified as hypofiltrating were significantly younger (by 4-to-11 months) compared with their peers assigned to the upper tail of eGFR distribution (Table 4). With the height-independent equations, males presenting eGFR $\leq 5^{\text{th}}$ percentile were taller. The opposite was observed employing the height-dependent formulae; with the FAS-QH equation, the means differed by almost 18 cm (Table 4).

Using Léger's and LM-LBM equations, the prevalence of central obesity, general overweight/obesity, elevated blood pressure (BP), low high-density lipoprotein cholesterol (HDL-C), elevated atherogenic index, and C reactive protein (CRP) > 3 mg/L was significantly higher in males at the upper tail of eGFR distribution vs. the lower tail (Table 5). The prevalence of general obesity was also higher by Sch-L and FAS-QA formulae; while

all but FAS-QA equations indicated a higher prevalence of elevated fasting insulin in subjects with eGFR $\geq 95^{\text{th}}$ percentile. The prevalence of elevated triacylglycerols, uric acid, and that of microalbuminuria did not differ between the groups (Table 5).

With the LM-LBM formula, females at the upper tail of eGFR distribution were by about 5 months younger than their peers at the lower tail, the FAS-QA equation returned the opposite (Table 6). As in males, LM and FAS-QA equations indicated that females at the upper tail of distribution were shorter compared with their hypofiltrating peers, and the opposite was observed employing the height-dependent formulae. With the FAS-QH equation, the height difference reached about 14 cm.

Using the FAS-QA formula, females manifesting eGFR $\leq 5^{\text{th}}$ percentile more likely suffered from hyperuricemia than their counterparts with eGFR $\geq 95^{\text{th}}$ percentile (Table 6). Léger's and LM-LBM equations indicated a higher prevalence of central obesity, general overweight/obesity or obesity, elevated fasting insulin, and CRP levels, and low HDL-C in females at the upper tails of eGFR distributions compared with those on the lower ones. None of the equations indicated a difference in the prevalence of elevated BP, hypertriacylglycerolemia, elevated atherogenic index, or microalbuminuria.

Discussion

We explored the extent of agreement between six creatinine-based formulae for estimation of GFR in a cohort of apparently healthy adolescents, with the intent to explore which equations match the best in the classification of hyperfiltration and hypofiltration. As expected, different formulae returned a broad range of eGFR values, with higher differences across eGFR percentiles in males than females. Only in females, we revealed a pair of equations - Léger's and LM-LBM formulae - showing the clinically acceptable match in assigning the subjects into both, the lower and the upper tail of eGFR distribution. However, only females classified by these equations as hyperfiltrating, manifested a higher prevalence of obesity and obesity-associated comorbidities compared with their hypofiltrating peers. Except for a moderately higher prevalence of hyperuricemia in females with GFR $\leq 5^{\text{th}}$ percentile indicated by the FAS-QA formula, adolescents assigned into the lower eGFR tails did not present an increased prevalence of comorbid conditions consistent with chronic kidney disease (CKD).

In line with former studies in healthy or T1D adolescents¹³⁻¹⁵, also in our study different pediatric formulae returned diverse mean eGFR values. Five out of six equations indicated sex differences in mean eGFR - but neither consistently regarding whether mean eGFR was higher in males or females, nor completely matching the sex differences reported by Boettcher et al. for a large group of children and adolescents with T1D¹⁵. The

difference between the highest and the lowest mean eGFR in our study was similar to that reported for 12-to-17-year-old US adolescents ($43 \text{ mL/min/1.73 m}^2$)¹⁴ but higher than the difference of about $16 \text{ mL/min/1.73 m}^2$ in males, and $20 \text{ mL/min/1.73 m}^2$ in females observed in 1-to-<18-year-old T1D patients¹⁵.

Differences among serum creatinine-based formulae derived to estimate GFR in pediatric population stem from the differences in variables included in the equations (i.e., age, height, body weight, sex), mathematical forms and coefficients calculated to fit best the source data, e.g., the populations that were used to derive the equations. Among six formulae compared in our study, data on patients with kidney diseases served as sources in the construction of four of them. Schwartz-Lyon¹⁸ and Léger's¹⁹ formulae were derived from pediatric patients with CKD, or CKD and kidney transplanted patients, respectively. The LM and LM-LBM equations were developed from data on adults mostly with renal disease²⁰, and later they were evaluated in a pediatric cohort consisting mainly of subjects with suspected or confirmed CKD²¹. It has been suggested that as in adults, also in children and adolescents equations developed in populations with decreased GFR underestimate GFR among those without kidney disease¹⁴. However, in our cohort, Léger's formula consistently overestimated eGFR compared with values returned by FAS-QA and FAS-QH equations in both sexes; and in females, LM-LBM gave slightly higher eGFR means than both FAS formulae between the 1st to about 25th percentile. It is assumed that variations in creatininemia in patients with CKD are more likely to reflect changes in GFR; while muscle mass, growth, or protein intake are more important determinants of serum creatinine levels in subjects without CKD. In our study, the LM equation gave the lowest eGFR among the six formulae throughout the whole range of creatinine values in both sexes, and thus the highest prevalence (>40%) of subjects with hypofiltration (eGFR $<75 \text{ mL/min/1.73 m}^2$), followed by the Sch-L formula. This is in line with data on 1-to-<18-year-old males with T1D; while in females the Sch-L formula gave lower means compared with the LM equation¹⁵. As in the study of Boettcher et al.¹⁵, the introduction of lean body mass component into the LM equation returned higher mean eGFR compared with the LM equation. However, with GFR above $110 \text{ mL/min/1.73 m}^2$, the overestimation of eGFR by LM-LBM equation compared with LM and Sch-L formulae gradually diminished (Fig. 1a and 1b). Although both LM equations were derived from the same population, their course across eGFR percentiles was not parallel. Léger's¹⁹ formula returned the highest eGFR values throughout the whole serum creatinine range, and showed the steepest rise across the percentiles, reaching a difference of $100 \text{ mL/min/1.73 m}^2$ in males, and $80 \text{ mL/min/1.73 m}^2$ in females. With the other formulae derived from patients with CKD, differences between the 1st and the 99th eGFR percentile varied between $50\text{-}60 \text{ mL/min/1.73 m}^2$ in males, and $40\text{-}50 \text{ mL/min/1.73 m}^2$ in females. Nonetheless, for Léger's equation, the study in US adolescents reported a similar

difference in eGFR (about 120 mL/min/1.73 m²) across the percentiles ¹⁴ as observed by us. Of note, creatininemia ranged about 45-to-100 µmol/L in both studies.

The FAS-QA and FAS-QH formulae intended to provide equations for all ages, without the discontinuity between pediatric and adult equations, based on Belgian data on 0.1-to-20-year-old healthy subjects ¹⁶. The FAS-QA formula enables eGFR calculation in case the anthropometric data is not available. In line with findings in adolescents with T1D ¹⁵, in our females both FAS equations returned similar mean eGFR; while in males mean FAS-QH eGFR was slightly higher than that given by FAS-QA. In both sexes, the FAS-QA formula overestimated eGFR in comparison with the LM and Sch-L formulae, but the rise in eGFR across the percentiles was similar. FAS-QH formula-derived eGFR rose sharply across the percentiles - particularly in males, in whom the difference across the percentiles corresponded to that observed for Léger's equation and at the upper end of distribution two formulae returned almost identical eGFR values. This finding is surprising, as it has been assumed that eGFR values returned by equations based on data from patients with renal disease differ from those derived from healthy subjects ⁴; and that the FAS-QH equation outperforms the other height-dependent formulae in healthy adolescents ¹⁶. Likewise, the discrepancy between FAS-QA and FAS-QH formulae, particularly in our males, is surprising. It suggests that a single normalization constant derived from a population of healthy Belgian adolescents might not be representative of other European adolescents.

Theoretically, numerically different eGFR values returned by different formulae would not be confounding if reported along with age- and sex-specific reference ranges. Knowing which formula had been used, and what are the particular cut-offs, the clinician or epidemiologist provided with a simple eGFR value would be able to judge whether an individual should be subjected to further diagnostic steps. However, this assumption would be plausible only if different formulae consistently classify the same subject as hypofiltrating or hyperfiltrating. This requirement is important for both general practice and epidemiological studies, as subjects with low or high eGFR should be referred for further examination to confirm or reject kidney disease. Our data suggest that in apparently healthy adolescents, a conventional cut-off limit for hypofiltration or hyperfiltration cannot be universally applied. The LM formula-derived eGFR yielded extremely high frequencies of eGFR ≤75 mL/min/1.73 m² in both sexes and the Sch-L formula probably also overestimated the prevalence in our males; while applying the other formulae, the frequencies of abnormal eGFR were low and corresponded with those reported for the general population of adolescents in other studies ^{14,17}. On the other hand, Léger's and FAS-QH yielded a very high prevalence of eGFR ≥ 135 mL/min/1.73m² in both sexes; while Sch-L, LM, and LM-LBM hardly identified a single hyperfiltrating individual.

Similarly, a concordance of six formulae in assigning the same subject to the lowest or the highest 5% of eGFR distribution was poor. In both sexes, among fifteen possible pairs between six formulae, the coefficient of determination $\geq 90\%$ was revealed for three pairs (LM vs. Sch-L or FAS-QA, and Léger vs. LM-LBM). However, overall correlations seemed not to be sensitive enough to detect variations occurring at the extremities of the distribution. While in females these three pairs of equations showed also acceptable matching ($\geq 80\%$) for assigning the probands into the lowest tail of eGFR distribution; in males, it was only LM vs. FAS-QA, and additionally the Sch-L vs. LM-LBM pair. The differences in eGFR calculated by different formulae increase with higher eGFR^{13,14}. However, we show that even the values at the 5th percentile are diverse: the height-independent formulae (LM and FAS-QA) showing an acceptable matching for classification of hypofiltration in both sexes, return at the 5th percentile values differing by ≥ 20 mL/min/1.73 m². Regarding hyperfiltration, LM vs. Sch-L, and Léger's formula vs. the LM-LMB showed $\geq 80\%$ matching in adolescent males; in females, only the latter pair returned acceptable concordance. Our data do not support our hypothesis on the consistent classification of subjects to the lower or the upper tail of eGFR distribution by formulae derived from the same populations. As in apparently healthy adolescents, eGFR results indicating hypofiltration or hyperfiltration as estimated by different creatinine-based formulae are equivocal, interpretation of the results must be done with caution. This underscores the importance of clinical decision-making, which includes multiple factors in addition to eGFR²². Our data suggest that the question on the reliability of different formulae in the estimation of GFR²³ is not restricted to adults.

Except for the fact that both height-independent formulae assigned shorter individuals into the lower tail of eGFR distributions; and that the FAS-QA equation indicated a moderately higher prevalence of hyperuricemia in females with eGFR $\leq 5^{\text{th}}$ percentile compared with those within the upper 5%, no group of participants with eGFR $\leq 5^{\text{th}}$ percentile showed an increased prevalence of other conditions consistent with CKD. These findings are in line with those reported for US adolescents in the lower ranges of eGFR¹⁴. On the other hand, using Léger's and LM-LBM formulae, hyperfiltrating subjects of both sexes presented a higher prevalence of general and central obesity, dyslipidemia, fasting hyperinsulinemia, and CRP > 3 mg/L compared with their hypofiltrating peers. The US study in non-diabetic adolescents also reported an association of glomerular hyperfiltration with hypertriglycerolemia and lower insulin sensitivity²⁴.

The strengths of our study are a reasonably large sample of White Caucasian adolescents in whom data were gathered within one year, that morphometry was performed by trained staff according to the same protocol, and serum samples were analyzed in a central laboratory referencing creatinine assay to IDMS standards. We do not

have data on renal or plasma creatinine clearance or the measured GFR; thus, we only could assess agreement between the formulae rather than which formula is most accurate. Observed associations might be biased by the potential participation of close relatives. Our results are based on a single measurement, we did not follow renal function status over time. There is a limitation of generalizing our findings to populations with different epidemiological, anthropometric or clinical characteristics.

In conclusion, our data show that relationships between eGFR values returned by pediatric formulae are largely lax and the concordance of the equations in assigning apparently healthy adolescents as hypofiltrating or hyperfiltrating is generally poor. As we did not follow renal function status over time, and to our knowledge, there is no data from other populations to compare potential discrepancies in the assignment of adolescents to tails of eGFR distributions, it remains questionable which eGFR formula should be used in adolescents to screen for abnormal renal function in general practice or epidemiological studies. This presents an opportunity for future studies in longitudinal cohorts.

Subjects and methods

This is a retrospective analysis of the data obtained in the cross-sectional study “Respect for Health”. The survey had been launched in cooperation of two local health authorities - The Department of Health of Bratislava Self-governing Region and the Regional Public Health Authority of the Slovak Republic in Bratislava - and aimed to characterize the cardiometabolic health status of students attending public secondary schools in Bratislava region. Data were collected between November 2011 and December 2012. Acute illness, pregnancy, or lactation in females were exclusion criteria. Complete data on anthropometry and blood chemistry were obtained from 2,960 students aged 12–23 years. For the current analysis, we extracted data on 14-to-17-year-old White Caucasian adolescents of Central European descent (n = 1,993; 53.4% females).

The study was conducted according to The Declaration of Helsinki, after the approval of the protocol by the Ethics Committee of Bratislava Self-Governing Region. The decision to participate was voluntary. Signed informed consent was obtained from parents or legal guardians of participants.

Measurements. The study protocol has been explained in detail previously ²⁵. Briefly, height, body weight, and blood pressure measurements were performed directly at high schools by trained staff, according to standard protocols ²⁵. Body mass index (BMI) and waist-to-height ratio (WHtR) were calculated.

At appointed health centers, blood samples were collected after overnight fasting. Serum concentrations of glucose, HDL-C, triacylglycerols, high-sensitive CRP, insulin, and uric acid were analyzed in a central

laboratory using standard analytical methods (ADVIA 2400 analyzer, Siemens, Erlangen, Germany). Serum creatinine was analyzed via compensated, rate-blanked Jaffé reaction, with isotope dilution mass spectrometry (IDMS)-traceable calibrator (National Institute of Standards and technology, SRM 967). In spot urine, albumin (turbidimetrically) and creatinine concentrations were determined, and urinary albumin-to-creatinine ratio (ACR) was calculated.

Estimation of glomerular filtration rate. Serum creatinine derived glomerular filtration rate (eGFR) was estimated using six formulae, i.e., the Schwartz-Lyon formula¹⁸, the formula of Léger et al.¹⁹, the revised Lund-Malmö formula²⁶, the Lund-Malmö formula with lean body mass extension²⁰, and the full-age spectrum with Q-age or with Q-height extension¹⁶, as follows:

Schwarz-Lyon formula (SCh-L)¹⁸

$$= k * (height[cm]/sCrea[\mu mol/L])$$
 k=36.5 in males aged >13 years
 k=32.5 in others

Léger's formula¹⁹

$$= 56.7 * weight[kg] + 0.142 * heigh[cm]^2/sCrea[\mu mol/L]$$

Lund-Malmö formula (LM)²⁶

$$= e^{X-0.0158*age+0.438*\ln(age)}$$
 Males:
 X = 2.56 + 0.00968*(180-sCrea[μmol/L]), if sCrea<180 μmol/L
 X = 2.56 - 0.926*ln(sCrea[μmol/L]/180), if sCrea≥180 μmol/L
 Females:
 X = 2.50 + 0.0121*(150-sCrea[μmol/L]), if sCrea<150 μmol/L
 X = 2.50 - 0.926*ln(sCrea[μmol/L]/150), if sCrea≥150 μmol/L

Lund-Malmö formula with lean body mass extension (LM-LBM)²⁶

$$= e^{X-0.00587*age+0.00977*LBM}$$
 X = 4.95 - 0.0110*sCrea[μmol/L], if sCrea<150 μmol/L
 X = 8.58 + 0.0005*sCrea[μmol/L] - 1.08*ln(sCrea[μmol/L]), if sCrea≥150 μmol/L
 Lean body mass (LBM):
 Males: LBM = 1.10* weight [kg] - 120*(weight [kg]/height [cm])²
 Females: LBM = 1.07*weight [kg] - 148*(weight [kg]/height [cm])²

Full-age spectrum formula with Q-height extension (FAS-QH)¹⁶

$$= 107.3/(sCrea[mg/dL]/Q)$$

$$Q = 3.94 - 13.4*(height [m]) + 17.6*(height [m])^2 - 9.84*(height [m])^3 + 2.04*(height [m])^4$$

Full-age spectrum formula with Q-age extension (FAS-QA)¹⁶

$$= 107.3/(sCrea[mg/dL]/Q)$$
 Males: Q = 0.21 + 0.057*age - 0.0075*age² + 0.00064*age³ - 0.000016*age⁴
 Females: Q = 0.23 + 0.034*age - 0.0018*age² + 0.00017*age³ - 0.0000051*age⁴

eGFR is expressed in mL/min/1.73 m², height is expressed in centimeter (cm) except for FAS-QH formula, where it expressed in meter (m), sCrea: serum creatinine concentration expressed in micromoles per liter (μmol/L), except for FAS formulae, where it is expressed in mg/dL (conversion factor: 88.42), age is expressed in years, body weight in kilograms, Ln: natural logarithm, e: the base of the natural logarithm

Arbitrarily, hypofiltration and hyperfiltration were set at the formula- and sex-specific $\leq 5^{\text{th}}$ and $\geq 95^{\text{th}}$ eGFR percentile, respectively. We also used the conventional cut-offs: ≤ 75 mL/min/1.73m² and ≥ 135 mL/min/1.73m², as recommended for adolescents^{17,27}.

Definition of cardiometabolic risk factors. The presence of general overweight and obesity was classified using the international age- and sex-specific cutoff points²⁸, that of central obesity as WHtR ≥ 0.5 ²⁹. Presence of elevated systolic BP (SBP ≥ 130 mmHg) or diastolic BP (DBP ≥ 85 mmHg); elevated triacylglycerols (TAG ≥ 1.7 mmol/L), low HDL-C (males: < 1.03 mmol/L, females: < 1.29 mmol/L); increased atherogenic index of plasma (= $\log(\text{TAG}/\text{HDL-C}) \geq 0.11$ ³⁰, fasting glycemia (≥ 5.6 mmol/L), elevated uric acid levels (≥ 340 $\mu\text{mol/L}$ in females, ≥ 420 $\mu\text{mol/L}$ in males), concentration of fasting insulin ≥ 20 $\mu\text{IU/mL}$ ³¹, or CRP > 3 mg/L³² were considered as markers of increased cardiometabolic risk. Microalbuminuria was classified as ACR 2.5-25.0 mg/mmol in males and 3.5–35.0 mg/mmol in females³³.

Statistics. The descriptive characteristic of eGFR obtained by different formulae is given as the mean, SD, the 5th and 95th percentile, separately for males and females. The prevalence of subjects presenting eGFR under or above the conventional cut-offs for hypofiltration and hyperfiltration in adolescents is given as count and percentage. Between-sex differences in GFR estimated by different formulae were compared using the two-sided unpaired Student's t-test. Mutual regressions of eGFR values obtained by six equations were expressed as coefficients of determination (R^2). The agreement of different formulae in returning individuals' eGFR within the lower or upper tail of eGFR distribution, i.e., $\leq 5^{\text{th}}$ or $\geq 95^{\text{th}}$ percentile, was examined either as a match of designation by all six equations or pair-wise. Fisher's exact test was used to compare the prevalence of cardiometabolic risk factors between subjects within the lower and the upper tail of each eGFR distribution. Data are presented as means or as counts. P value < 0.05 was considered statistically significant. Analyses were performed by using the SPSS v.16 for Windows software (SPSS Inc., Chicago, IL, USA).

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Author contributions KS and RG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Study concept and design: KS and LP; Acquisition of data: KS, RG, LT; Analysis or interpretation of data: All authors; Drafting of the manuscript: KS, RG; Critical revision of the manuscript for important intellectual content: All authors.; Statistical analysis: KS and RG; Study supervision: KS.

Conflict of interest. All authors declare that they have no conflict of interest.

Ethical approval This study involved human participants and was reviewed and approved by the Ethics Committee of Bratislava Self-Governing Region. Written informed consent to participate was provided by the participant's parents or legal guardians.

Data availability Data that support the findings of this study are available from the corresponding author on reasonable request.

Table 1 Descriptive characteristics of estimated glomerular filtration rate returned by six creatinine-based formulae in males and females

Males						
eGFR formula	SCh-L	Léger	LM	LM-LBM	FAS-QH	FAS-QA
Mean	89.2	118.6	78.0	95.4	112.5	101.1
Standard deviation	12.9	20.8	11.8	12.0	22.0	14.1
5 th percentile	71.1	90.6	61.5	78.0	83.2	81.5
95 th percentile	111.7	155.1	98.8	114.1	153.6	125.8
≤75 mL/min/1.73m ² , n (%)	98 (10.5)	5 (0.5)	398 (42.8)	26 (2.8)	16 (1.7)	11 (1.2)
≥135 mL/min/1.73m ² , n (%)	4 (0.4)	175 (18.8)	1 (0.1)	1 (0.1)	135 (14.5)	14 (1.5)
Females						
eGFR formula	SCh-L	Léger	LM	LM-LBM	FAS-QH	FAS-QA
Mean	89.8	121.6	76.5	101.8	107.5	105.2
Standard deviation	11.3	18.6	10.0	9.1	16.0	13.4
P (vs. males)	0.276	0.001	0.002	<0.001	<0.001	<0.001
5 th percentile	72.7	94.7	61.8	86.9	84.5	85.4
95 th percentile	108.9	155.3	93.4	116.8	137.9	128.7
≤75 mL/min/1.73m ² , n (%)	80 (7.5)	0	499 (46.9)	3 (0.3)	6 (0.6)	4 (0.4)
≥135 mL/min/1.73m ² , n (%)	1 (0.1)	229 (21.5)	1 (0.1)	1 (0.1)	64 (6.3)	21 (2.1)

eGFR estimated glomerular filtration rate, SCh-L Schwarz-Lyon formula, LM Lund-Malmö formula, LM-LBM Lund-Malmö formula with lean body mass extension, FAS-QH the full-age spectrum formula with Q-height extension, FAS-QA the full-age spectrum formula with Q-age extension, significant p is given in bold

Table 2 Coefficients of determination between estimated glomerular filtration rate returned by six formulae in males (right upper corner) and females (lower-left corner)

	SCh-L	Léger	LM	LM-LBM	FAS-QH	FAS-QA
SCh-L	--	0.691	0.925	0.846	0.637	0.841
Léger	0.712	--	0.534	0.912	0.679	0.507
LM	0.910	0.546	--	0.736	0.377	0.916
LM-LBM	0.830	0.929	0.709	--	0.643	0.674
FAS-QH	0.815	0.731	0.551	0.736	--	0.507
FAS-QA	0.872	0.523	0.976	0.669	0.523	--

SCh-L Schwarz-Lyon formula, LM Lund-Malmö formula, LM-LBM Lund-Malmö formula with lean body mass extension, FAS-QH the full-age spectrum formula with Q-height extension, FAS-QA the full-age spectrum formula with Q-age extension

Table 3 Consistency between pairs of equations in assigning males and females into the $\leq 5^{\text{th}}$ percentile (the upper right corner) and into the $\geq 95^{\text{th}}$ percentile (the lower-left corner) of each eGFR distribution

Males						
	Sch-L	Léger	LM	LM-LBM	FAS-QH	FAS-QA
Sch-L	--	61%	78%	80%	63%	67%
Léger	48%	--	48%	72%	72%	43%
LM	83%	39%	--	70%	46%	80%
LM-LBM	59%	85%	48%	--	67%	65%
FAS-QH	46%	48%	30%	52%	--	43%
FAS-QA	67%	37%	76%	44%	28%	--
Females						
	SCh-L	Léger	LM	LM-LBM	FAS-QH	FAS-QA
SCh-L	--	62%	83%	74%	71%	69%
Léger	57%	--	49%	83%	67%	42%
LM	68%	40%	--	62%	54%	87%
LM-LBM	57%	94%	40%	--	67%	53%
FAS-QH	70%	53%	45%	55%	--	42%
FAS-QA	70%	42%	79%	42%	47%	--

eGFR estimated glomerular filtration rate, *SCh-L* Schwarz-Lyon formula, *LM* Lund-Malmö formula, *LM-LBM* Lund-Malmö formula with lean body mass extension, *FAS-QH* the full-age spectrum formula with Q-height extension, *FAS-QA* the full-age spectrum formula with Q-age extension

Table 4 Mean estimated glomerular filtration rate, mean age, and mean height of males and females assigned by six formulae to the lower ($\leq 5^{\text{th}}$) and the upper ($\geq 95^{\text{th}}$) tail of each distribution

Males									
Formula	eGFR, mL/min/1.73m ²			Age, years			Height, cm		
	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p
	$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$	
Sch-L	65	120	<0.001	16.4	15.5	<0.001	176.3	178.3	0.215
Léger	82	172	<0.001	16.3	15.8	0.013	173.1	183.3	<0.001
LM	56	106	<0.001	16.4	15.5	<0.001	181.3	175.0	<0.001
LM-LBM	70	121	<0.001	16.4	16.7	<0.001	176.4	182.7	<0.001
FAS-QH	75	168	<0.001	16.3	15.9	0.055	171.2	189.1	<0.001
FAS-QA	74	134	<0.001	16.0	16.0	1.000	181.3	175.7	0.001

Females									
Formula	eGFR, mL/min/1.73m ²			Age, years			Height, cm		
	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p
	$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$	
Sch-L	82	133	<0.001	16.4	16.2	0.101	164.5	168.8	<0.001
Léger	85	127	<0.001	16.3	16.1	0.155	161.9	169.9	<0.001
LM	81	135	<0.001	16.2	16.1	0.337	167.3	163.6	0.002
LM-LBM	84	127	<0.001	16.4	16.0	0.016	163.9	169.7	<0.001
FAS-QH	86	125	<0.001	16.3	16.0	0.075	160.6	174.4	<0.001
FAS-QA	81	136	<0.001	15.9	16.4	0.002	168.0	164.5	0.003

eGFR estimated glomerular filtration rate, *Sch-L* Schwarz-Lyon formula, *LM* Lund-Malmö formula, *LM-LBM* Lund-Malmö formula with lean body mass extension, *FAS-QH* the full-age spectrum formula with Q-height extension, *FAS-QA* the full-age spectrum formula with Q-age extension, significant p is given in bold

Table 5 The prevalence of cardiometabolic risk factors in males with estimated glomerular filtration rate $\leq 5^{\text{th}}$ vs. that of $\geq 95^{\text{th}}$ according to six creatinine-based equations

Formula	WHR ≥ 0.5			BMI Ow/Ob OITF			BMI Ob IOTF			SBP ≥ 130 or DBP ≥ 85 mm Hg			Glycemia ≥ 5.6 mmol/L			Insulin ≥ 20 $\mu\text{UI/mL}$		
	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p
Sch-L	4	10	0.145	15	18	0.664	1	8	0.030	10	9	1.000	2	2	1.000	2	11	0.014
Léger	1	129	<0.001	6	39	<0.001	0	25	<0.001	5	19	0.002	3	2	1.000	3	21	<0.001
LM	4	10	0.089	15	16	0.828	2	8	0.050	12	7	0.304	3	1	0.617	3	10	0.040
LM-LBM	3	22	<0.001	10	35	<0.001	1	18	<0.001	9	17	0.104	3	2	1.000	3	17	0.001
FAS-QH	4	8	0.345	12	18	0.266	1	7	0.059	9	20	0.024	3	2	1.000	1	11	0.004
FAS-QA	3	10	0.069	13	14	1.000	1	8	0.030	11	10	1.000	2	2	1.000	3	10	0.069
Formula	HDL-C < 1.29 mmol/L			TAG ≥ 1.7 mmol/L			AIP ≥ 0.11			Uric acid ≥ 420 $\mu\text{mol/L}$			ACR ≥ 2.5 mg/mmol			CRP > 3 mg/L		
	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p	eGFR perc. $\leq 5^{\text{th}}$	eGFR perc. $\geq 95^{\text{th}}$	p
Sch-L	8	8	1.000	0	3	0.242	2	5	0.434	7	3	0.315	2	2	1.000	2	8	0.090
Léger	8	19	0.021	1	6	0.111	1	11	0.004	5	11	0.168	1	0	1.000	1	9	0.015
LM	9	8	1.000	2	3	0.677	3	5	0.486	8	2	0.091	2	3	0.677	1	6	0.059
LM-LBM	9	16	0.159	2	6	0.267	2	10	0.027	6	9	0.574	2	0	0.495	1	8	0.030
FAS-QH	8	10	0.793	1	2	1.000	2	4	0.677	9	4	0.231	1	2	1.000	2	6	0.267
FAS-QA	10	8	0.793	2	3	1.000	2	5	0.434	10	3	0.069	1	2	1.000	2	8	0.090

The prevalence is given as the number of males presenting the risk factor out of 46/group

Formulae: *Sch-L* Schwarz-Lyon, *LM* Lund-Malmo, *LM-LBM* Lund-Malmo with lean body mass, *FAS-QH* Full-age Spectrum with Q-height, *FAS-QA* Full-age Spectrum with Q-age *WHR* waist-to-height ratio, *BMI* body mass index, *ow/ob* overweight/obese, *OITF* The International Obesity Taskforce, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *TAG* triacylglycerols, *AIP* atherogenic index of plasma, *ACR* urinary albumin-to-creatinine ratio, *CRP* C-reactive protein, significant p is given in bold

Table 6 The prevalence of cardiometabolic risk factors in females with estimated glomerular filtration rate $\leq 5^{\text{th}}$ vs. that of $\geq 95^{\text{th}}$ according to six creatinine-based equations

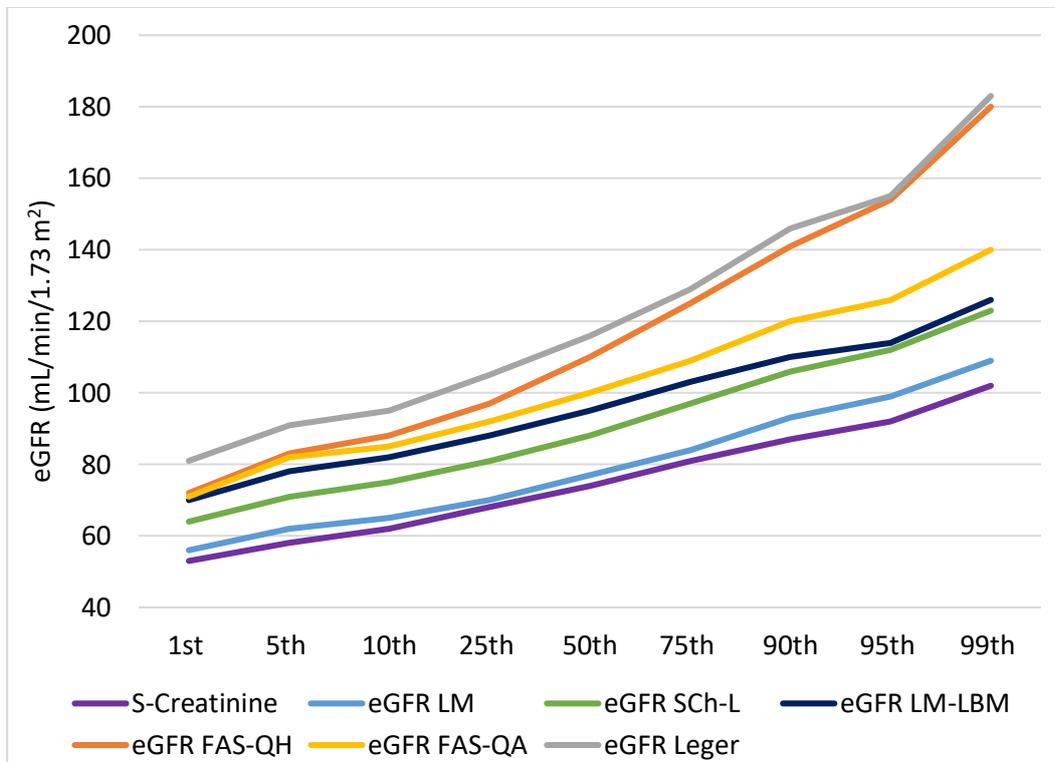
Formula	WHR ≥ 0.5			BMI Ow/Ob OITF			BMI Ob IOTF			SBP ≥ 130 or DBP ≥ 85 mm Hg			Glycemia ≥ 5.6 mmol/L			Insulin ≥ 20 $\mu\text{UI/mL}$		
	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p	eGFR perc.		p
	$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$	
Sch-L	1	4	0.363	9	8	0.797	0	2	0.495	3	1	0.363	2	2	1.000	0	4	0.118
Leger	1	17	<0.001	1	30	<0.001	0	11	0.001	4	3	1.000	2	2	1.000	1	9	0.016
LM	1	7	0.060	6	11	0.290	0	2	0.495	4	0	0.118	1	2	1.000	0	4	0.118
LM-LBM	1	16	<0.001	2	29	<0.001	0	10	0.001	3	3	1.000	2	2	1.000	0	9	0.003
FAS-QH	2	4	0.697	10	6	0.286	0	1	1.000	3	2	0.675	1	2	1.000	0	3	0.243
FAS-QA	0	5	0.057	6	9	0.579	0	3	0.243	4	1	0.363	1	1	1.000	0	4	0.118
Formula	HDL-C < 1.29 mmol/L			TAG ≥ 1.7 mmol/L			AIP ≥ 0.11			UA ≥ 340 $\mu\text{mol/L}$			ACR ≥ 3.5 mg/mmol			CRP > 3 mg/L		
	eGFR perc		p	eGFR perc		p	eGFR perc		p	eGFR perc		p	eGFR perc		p	eGFR perc		p
	$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$		$\leq 5^{\text{th}}$	$\geq 95^{\text{th}}$	
Sch-L	9	17	0.131	4	1	0.205	2	2	1.000	8	2	0.052	2	2	1.000	5	8	0.555
Leger	5	22	<0.001	2	3	1.000	1	5	0.205	7	5	0.761	4	0	0.118	5	14	0.041
LM	9	18	0.073	3	1	0.618	2	1	1.000	9	3	0.123	2	2	1.000	4	7	0.526
LM-LBM	5	20	0.001	2	3	1.000	1	5	0.205	8	5	0.555	3	0	0.243	4	13	0.032
FAS-QH	7	15	0.094	2	1	0.614	0	2	0.495	4	2	0.433	2	2	1.000	2	6	0.271
FAS-QA	8	17	0.066	3	1	0.618	2	1	1.000	10	2	0.028	2	1	1.000	4	7	0.526

The prevalence is given as the number of males presenting the risk factor out of 53/group

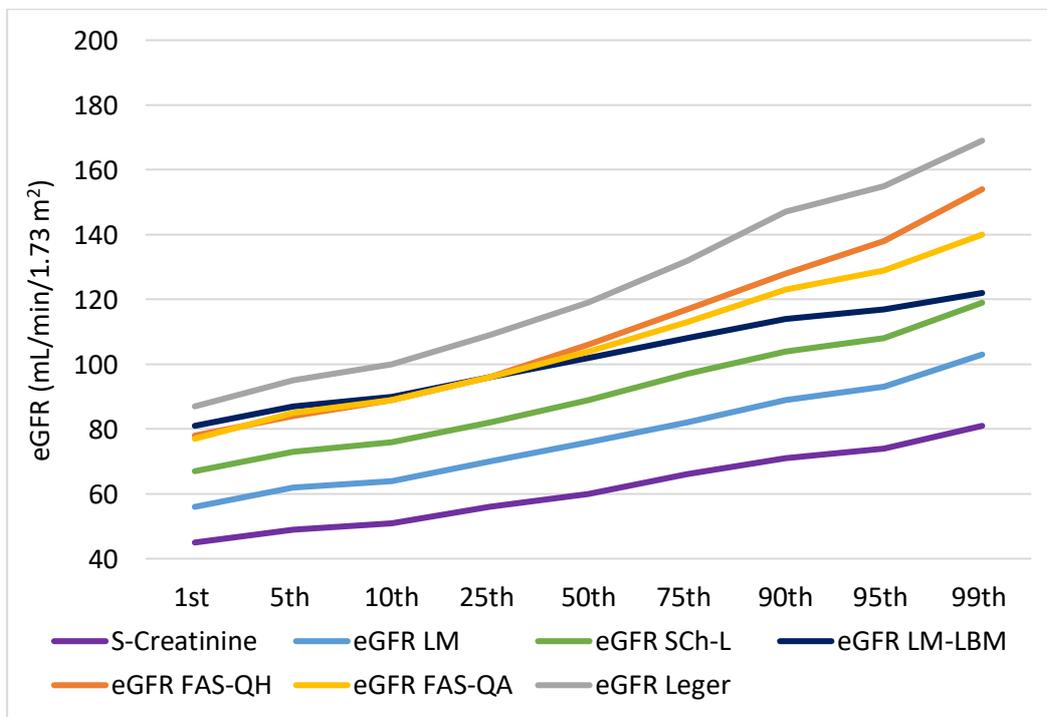
Formulae: *Sch-L* Schwarz-Lyon, *LM* Lund-Malmo, *LM-LBM* Lund-Malmo with lean body mass, *FAS-QH* Full-age Spectrum with Q-height, *FAS-QA* Full-age Spectrum with Q-age
WHR waist-to-height ratio, *BMI* body mass index, *ow/ob* overweight/obese, *OITF* The International Obesity Taskforce, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *TAG* triacylglycerols, *AIP* atherogenic index of plasma, *ACR* urinary albumin-to-creatinine ratio, *CRP* C-reactive protein, significant p is given in bold

Fig. 1 Chart-flow of serum creatinine concentration and estimated glomerular filtration rate values returned by six formulae across 1st to 99th percentile in A/ males and B/ females

A/



B/



eGFR estimated glomerular filtration rate, *SCh-L* Schwarz-Lyon formula, *LM* Lund-Malmö formula, *LM-LBM* Lund-Malmö formula with lean body mass extension, *FAS-QH* the full-age spectrum formula with Q-height extension, *FAS-QA* the full-age spectrum formula with Q-age extension

Figures

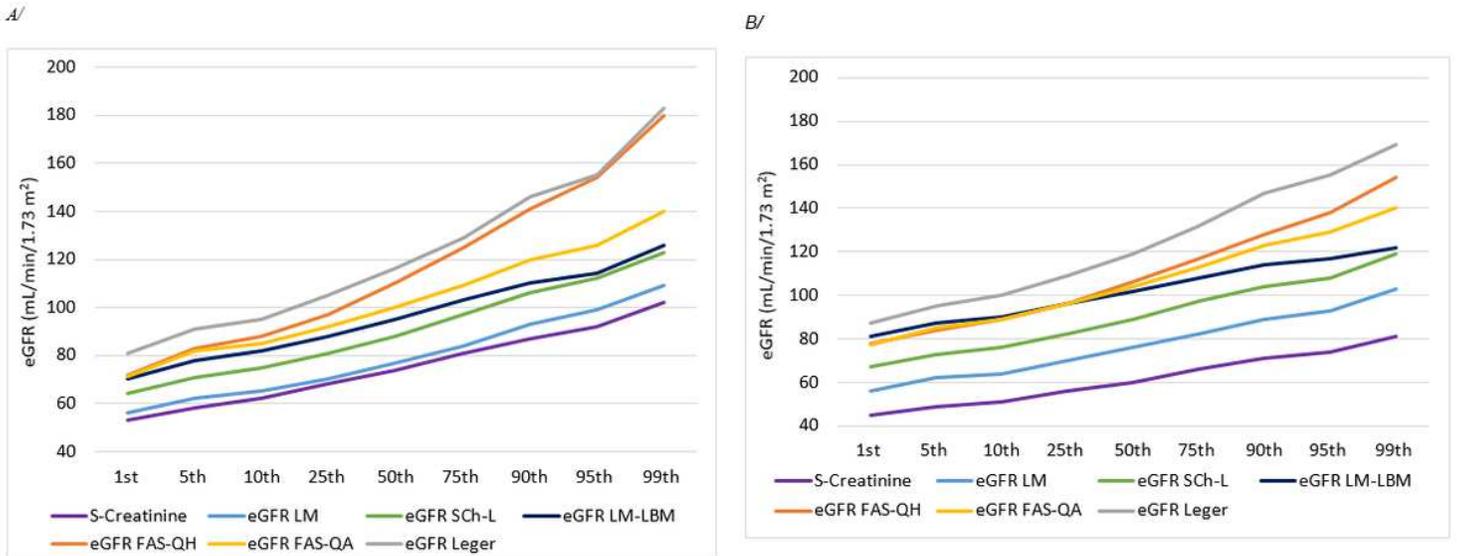


Figure 1

Chart-flow of serum creatinine concentration and estimated glomerular filtration rate values returned by six formulae across 1st to 99th percentile in A/ males and B/ females eGFR estimated glomerular filtration rate, SCh-L Schwarz-Lyon formula, LM Lund-Malmö formula, LM-LBM Lund-Malmö formula with lean body mass extension, FAS-QH the full-age spectrum formula with Q-height extension, FAS-QA the full-age spectrum formula with Q-age extension