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REVIEW ARTICLE

Influence of ethnicity on population reference values for biochemical markers

Houman Tahmasebi[a,b], Karin Trajcevski[a], Victoria Higgins[a,b] and Khosrow Adeli[a,b]

[a]CALIPER Program, Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada; [b]Department of Laboratory Medicine & Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Canada

ABSTRACT

Reference intervals (RIs) for biochemical and hematological markers determined using healthy adult and/or pediatric populations are vital for clinical interpretation of laboratory test results. Most clinical laboratories commonly use age- and sex-specific RIs, but the effect of ethnicity as a covariate is often overlooked. Ethnic differences in serum biomarker concentrations can occur as a result of genetic and environmental factors, while the degree to which each factor influences serum levels depends on the specific biomarker. Numerous studies have investigated ethnic differences in routine chemistry, fertility, endocrine, cancer, and hematological markers, as well as in vitamins and carotenoids, in children, adolescents and adults. In the present review, we summarize and discuss ethnic-specific differences observed for these laboratory markers and their potential impact on the clinical interpretation of laboratory test results. We categorized the available data into seven major ethnic groups (i.e. Black, Caucasian, East Asian, Hispanic, South Asian, South East Asian, and West Asian) for ease of comparison. While certain biomarkers could not be compared between ethnic groups because of insufficient information or contradictory results between studies, significant differences between ethnic groups were reported by one or more studies for most of the biomarkers included in this review. The clinical significance of these differences and the potential need for ethnic-specific RIs for certain biochemical markers are also discussed.

Abbreviations: AACB: Australasian Association of Clinical Biochemists; ALT: alanine aminotransferase; AST: aspartate aminotransferase; apoA1: apolipoprotein A1; apoA2: apolipoprotein A2; apoB: apolipoprotein B; apoE: apolipoprotein E; BK: Black; BMI: body mass index; BT: bioavailable testosterone; CA: Caucasian; CALIPER: Canadian Laboratory Initiative on Paediatric Reference Intervals; CHILDx: Children's Health Improvement through Laboratory Diagnostics; CHMS: Canadian Health Measures Survey; CK: creatine kinase; CK-MB: creatine kinase muscle-brain fraction; CLSI: Clinical and Laboratory Standards Institute; CRP: C-reactive protein; cTnI: cardiac troponin I; CysC: cystatin C; EA: East Asian; FSH: follicle stimulating hormone; FT4: free thyroxine; GGT: gamma-glutamyltransferase; Hb: hemoglobin; HC: Hispanic; Hct: hematocrit; Hcy: homocysteine; HDL-C: high-density lipoprotein cholesterol; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMA: ischemia modified albumin; iPTH: intact parathyroid hormone; KiGGS: Health Interview and Examination Survey for Children and Adolescents; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MTHFR: methylenetetrahydrofolate reductase; NHANES: National Health and Nutrition Examination Survey; non-HDL-C: non-high-density lipoprotein cholesterol; NORIP: Nordic Reference Interval Project; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PSA: prostate specific antigen; PTH: parathyroid hormone; RI: reference interval; SA: South Asian; SEA: South East Asian; SES: socioeconomic status; SHBG: sex hormone-binding globulin; TCI: transcobalamin I; TG: triglycerides; TIBC: total iron binding capacity; TP: total protein; TSH: thyroid stimulating hormone; TT: total testosterone; TT3: total triiodothyronine; TT4: total thyroxine; UK: United Kingdom; US: United States; VDBP: vitamin D binding protein; WA: West Asian; WBC: white blood cell count

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1. Population reference intervals for biomarkers of health and disease

Laboratory medicine is fundamental to clinical decision-making, including diagnosis, prognosis, treatment, and/or patient management. Laboratory test results are most commonly interpreted using reference intervals (RIs), which are often defined as the central 95% of the distribution of laboratory test results obtained from a

CONTACT Khosrow Adeli khosrow.adeli@sickkids.ca Clinical Biochemistry, Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada

healthy reference population. Although the concept and utility of RIs are straightforward, their establishment is complex, time-consuming, and costly. As a result, critical gaps in population RIs, particularly for pediatric and geriatric populations, have contributed to major challenges in the accurate interpretation of laboratory test results by clinicians and other healthcare professionals. RIs should be established based on a population that is similar in all aspects to the patient, with the exception of the disease condition of interest. Therefore, a sufficiently large, representative, and healthy population must be selected using pre-defined inclusion and exclusion criteria. Additionally, pre-analytical and analytical processes must be sufficiently documented and adhere to quality control standards. Lastly, a robust statistical protocol must be followed to accurately determine RIs. To improve the accuracy and clinical applicability of RIs, they need to be partitioned based on covariates such as age, sex and ethnicity. The Clinical and Laboratory Standards Institute (CLSI) has published guidelines for defining and establishing RIs for use in clinical laboratories [1]. The extensive procedures required to determine accurate and robust RIs are often beyond the capabilities of individual laboratories. Therefore, many laboratories establish RIs inappropriately, using patient populations, limited sample sizes, or incorrect statistical procedures. Alternatively, others adopt RIs inappropriately from other laboratories or from manufacturer product inserts without first verifying them for their local population and analytical platform. In addition, many RIs used by laboratories do not consider covariates, especially ethnicity.

1.1. Recent reference interval initiatives

Several national initiatives have begun to address these critical gaps by accurately establishing RIs [2], including the Nordic Reference Interval Project (NORIP) in the Nordic countries [3–5], the Children's Health Improvement through Laboratory Diagnostics (CHILDx) in the United States (US) [6–8], the Australasian Association of Clinical Biochemists (AACB) in Australia and New Zealand [9,10], the Canadian Laboratory Initiative on Paediatric Reference Intervals (CALIPER) [11–14] in Canada, and the Health Interview and Examination Survey for Children and Adolescents (KiGGS) in Germany [15,16]. NORIP [3,5] and AACB [9] have recently established age- and sex-specific adult RIs, while KiGGS [15] and CHILDx [8] have established age- and sex-specific pediatric RIs. The CALIPER project in Canada has established age-, sex- and Tanner stage-specific pediatric RIs [12–14,17,18]. Additionally, in collaboration with the Canadian Health Measures Survey (CHMS), a program of Statistics Canada, CALIPER recently established age- and sex-specific RIs for Canadians aged 3 to <80 years of age [19–21].

Although these national RI initiatives have made significant strides toward improving laboratory test interpretation, improvements in RIs are warranted to make them more representative of the individuals being assessed. When there is high inter-individual variation in a laboratory test (i.e. results significantly vary between individuals), the derived RI can be wide and, as a result, not appropriate for all individuals. Several covariates, including age, sex, pubertal status, body mass index (BMI), and ethnicity, contribute to inter-individual variation. While a multitude of studies have begun to address the effect of age and sex by establishing age- and sex-specific RIs [5,9,12,15,22], there remains a critical gap in our understanding of the influence of other covariates such as ethnicity.

2. Ethnicity as a covariate

2.1. Defining ethnic groups

It is important to differentiate between "ethnicity" and "race" prior to examining ethnic differences, as these terms are often improperly used interchangeably [23,24]. "Race" refers to the skin color and other phenotypical features of a person. "Ethnicity" describes subpopulations or subcultures in addition to biological characteristics. In other words, "race" is a broad term that may result in the inclusion of numerous ethnic groups. Use of the term "race" has been discouraged in scientific writing because of the lack of clear association between race and various biological characteristics (e.g. behavior). Categorizing individuals based on ethnicity is more commonly used for biological analysis, as both genetic and environmental factors exhibit extensive similarity within each ethnic group. However, because of insufficient literature on ethnic differences in biomarker levels, we report a racial categorization for Caucasians and Blacks. Table 1 describes the race-ethnic categorization, terminology and countries of ethnic origin used throughout this review. We will discuss differences in biomarker concentrations examined between seven major ethnic-race categories: Black, Caucasian, East Asian, Hispanic, South Asian, South East Asian and West Asian. To allow for a comprehensible analysis of ethnic findings from different studies, throughout this review, most populations or countries have been described as their corresponding ethnic categories unless findings indicate intra-ethnic differences.

Table 1. Ethnic-race categories, their commonly used synonyms and countries of origin.

Ethnic/race category	Synonyms	Country of ethnic origin
Black	African American	African and Caribbean countries (only those with black skin color)
	African Caribbean	
	African Descendant	
	Non-Hispanic Black [25]	
Caucasian	White	European countries
	Non-Hispanic White [25]	
East Asian	Oriental	China
		Japan
		Korea
Hispanic	Latin American	Central American countries
	Mexican Americans [25]	Mexico
		South American countries
South Asian		Bangladesh
		Bhutan
		India
		Nepal
		Pakistan
		Sri Lanka
South East Asian		Burma
		Cambodia
		Indonesia
		Malaysia
		Philippines
		Singapore
		Taiwan
		Thailand
		Vietnam
West Asian	Middle Eastern	Afghanistan
	Arab	Iran
		Iraq
		Israel
		Jordan
		Lebanon
		Palestine
		Saudi Arabia
		Syria
		United Arab Emirate
		Yemen
		Turkey

Not all countries mentioned above are included in the studies mentioned in this review. The rightmost column lists the countries where the ethnic groups originated, and they are not necessarily the countries of origin of study participants.

2.2. Ethnic-specific differences in biomarker concentrations

Traditionally, RIs used in clinical laboratories have been determined using predominantly Caucasian reference individuals [12,25]. However, variances in biomarker values have been noted between ethnic groups, highlighting the importance of establishing and implementing ethnic-specific RIs for select biomarkers [11,25–29]. Using RIs established from a predominantly Caucasian population to interpret laboratory test results from a non-Caucasian or multi-ethnic patient population may lead to inaccurate interpretation of test results and, ultimately, missed diagnosis or misdiagnosis [25,30–32]. For example, creatine kinase (CK) is commonly used as a biomarker for monitoring statin-induced myopathy to determine whether an individual can safely undergo or continue statin therapy [31,33]. The median CK activity for healthy Black adult males and females is approximately double that of Caucasian adult males and females, respectively [31]; a similar ethnic difference was confirmed by other studies [34–36]. The lack of an appropriate ethnic-specific RI for Black patients could result in termination of statin treatment in the absence of muscle toxicity, simply because their CK levels are above a RI established using a predominantly Caucasian reference population [31]. In the absence of robust RIs that are ethnic-specific, clinicians are not able to provide the best possible healthcare for all patients.

Genetic and environmental factors [e.g. socioeconomic status (SES) and habitual diet] contribute to ethnic differences in biomarker concentrations [37–41]. However, the impact of these factors depends upon the biomarker in question [42–51]. For example, environmental factors largely account for differences in vitamin A concentration between ethnicities. Looker et al. reported that vitamin and mineral supplementation and SES accounted for the majority of differences in serum vitamin A concentration between Hispanic and non-Hispanic (i.e. Black and Caucasian) children [42]. Similarly, while eosinophil counts were previously shown to be higher in Blacks of African origin [43,52], eosinophil counts between Caucasians and Blacks living

in the same community (i.e. Britain) were found to not differ [43], suggesting that an environmental factor, potentially a parasitic infection [52], was responsible for the difference in eosinophil counts. Lastly, ethnic differences observed for several biomarkers are the result of both genetic and environmental factors. For example, differences between ethnicities for homocysteine (Hcy) have been accounted for by methylenetetrahydrofolate reductase (MTHFR) polymorphisms as well as dietary intake of folate, vitamin B6 and cobalamin (vitamin B12) [44–51]. Similarly, serum calcidiol (25-hydroxyvitamin D) levels are affected by sun exposure, diet, and skin pigmentation [53–59]. Lighter skin color is associated with higher calcidiol levels and, in fact, many genetic determinants of skin pigmentation are associated with serum calcidiol levels [60]. Given that both genetic and environmental factors can influence ethnic differences in biomarker concentration, it is important to consider lifestyle factors and region of residence when studying the influence of ethnicity on circulating levels of biomarkers of health and disease.

2.3. Comparison of ethnic-specific biomarker concentrations

Limited studies have established ethnic-specific RIs for two or more ethnic groups. Many of these studies used the large National Health and Nutrition Examination Survey (NHANES) database, collected from the US population, to establish ethnic-specific reference limits for serum non-high-density lipoprotein cholesterol (non-HDL-C) [61], mercury [62], thyroid stimulating hormone (TSH) [63], prostate specific antigen (PSA) [64] and other biochemical and hematological tests [25], mainly for Caucasians, Blacks, and Hispanics. Ichihara et al. also determined ethnic-specific RIs for two East Asian (i.e. Japanese and Chinese) and South East Asian populations for biomarkers with regional differences, and common Asian RIs in the absence of ethnic differences, for various common and specialized laboratory tests [65,66]. Although studies by Ichihara et al. indicated the presence of statistically significant differences between ethnicities, they did not report statistical differences of pair-wise comparisons between specific ethnic groups. Thus, for studies by Ichihara et al., relative differences in serum values between ethnicities have been reported in Section 3 based on subjective comparison of ethnic-specific RIs, including medians and upper and lower reference limits.

As previously mentioned, both genetic and environmental factors can influence serum levels of various biomarkers. Thus, it is preferable for each region to establish RIs specific for its own population as opposed to adopting RIs established in other countries with similar races/ethnicities. This becomes especially important for multi-ethnic regions (e.g. US and Canada), in which the reference population used to establish RIs should be representative of the multi-ethnic population to ensure accurate laboratory test interpretation and clinical diagnosis. Recruitment of individuals from the local population, as opposed to adopting RI from an individual's country of origin, is vital because of the influence of unique environmental factors associated with the country of residence. Thus, the limited availability of ethnic-specific RIs warrants further studies to determine differences in biomarker concentrations between ethnicities in multi-ethnic countries.

3. Evidence for ethnic differences in biomarker concentrations

Initially, a systematized literature review was conducted in 2016 using PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) to identify both pediatric and adult studies that have evaluated differences in serum biomarker levels between the ethnic groups indicated in Table 1. Three criteria (and their synonyms) were used to filter the search results: reference interval, ethnicity, and laboratory. Out of about 5700 articles found, approximately 500 were selected to be studied in greater detail because of their relevance to this project. The selection was then reduced to approximately 100 studies based on the appropriateness of their methodology, including participant recruitment, statistical procedures, and measured biomarkers. Furthermore, other studies were selected from elsewhere, where appropriate, to complement available findings gathered from the systematized review. Most selected studies compared ethnic groups within their study, rather than comparing their results to those from other studies. Overall, while a limited number of studies have established ethnic-specific RIs, numerous studies have examined differences in biomarker concentration between ethnic groups in both pediatric and adult populations. These include examination of routine chemistry markers, fertility hormones, endocrine markers, cancer markers, hematological markers, and vitamins and carotenoids. Reported ethnic differences in biomarker concentrations are discussed below and summarized in Table 2.

3.1. Routine chemistry markers

3.1.1. Electrolytes

Ethnic differences in electrolytes have been partly investigated to better understand reported ethnic differences

in physiology such as adrenocortical hypofunction and elevated levels of parathyroid hormone (PTH) in Blacks compared to Caucasians [67,68]. A number of studies have reported no significant difference between Caucasian and Black adults for electrolytes: sodium, calcium, magnesium, and chloride [67–69]. Additionally, Horn and Pesce reported no difference between adult Hispanics and two other ethnicities (i.e. Blacks and Caucasians) in all electrolytes studied (i.e. calcium, chloride, phosphorous, and sodium) [69]. Similarly, a number of studies reported no ethnic difference for adult potassium amongst various combinations of Blacks, Caucasians, Hispanics, and Asians (i.e. East, South, and South East Asians) [25,68,69]. However, adult potassium levels were reported by Brickman et al. to be higher in Blacks compared to Caucasians [67]. A lower upper limit for an adult calcium RI has been reported in Asians (i.e. East, South, and South East Asians) compared to Caucasians, Blacks, and Hispanics [25]. Furthermore, Ichihara et al. found no differences in sodium, potassium, chloride and calcium levels between East Asian and South East Asian adult populations [65]. While adult Blacks and Caucasians did not show ethnic differences in magnesium levels, in pediatrics CALIPER has reported that South Asians have lower magnesium levels than Caucasians and East Asians [12]. In contrast, CALIPER found calcium and phosphate not to differ between Caucasians, East Asians, and South Asians, which is similar to the majority of reports in adults [12]. Overall, more studies are required to compare Caucasian and Black population electrolyte levels with Asian populations. Furthermore, because only one pediatric study has investigated differences in electrolytes, more pediatric research is needed in this area.

3.1.2. Renal and hepatic markers

Numerous renal and hepatic biomarkers have been found to differ with ethnicity. In adults, the renal biomarkers, aldosterone and renin, have been reported to be higher in Caucasians compared to Blacks, which is suggestive of greater salt retention in Blacks [70]. In children and older adults, the renal biomarker, creatinine, was reported to be higher in Blacks than Caucasians [71,72] and Hispanics [72]. However, in adolescents the novel renal biomarker, cystatin C (CysC), which has been found to be less affected than creatinine by other factors, has been noted to be higher in Caucasians compared to Blacks and Hispanics [72]. Further investigations into pediatric and adult renal markers are needed to confirm these findings.

Ethnic differences for hepatic biomarkers have been analyzed by some studies. Reports on ethnic differences for adult total bilirubin levels are conflicting: some reports show no differences between adult Caucasians, Blacks, Hispanics, and Asians (i.e. East, South, and South East Asians) [25,69], while others suggest lower levels in Blacks compared to Caucasians, Hispanics, and Asians [73,74]. Aspartate aminotransferase (AST) levels were reported to be different between Caucasians and Hispanics, though only in males [69]. However, other studies found no ethnic difference in AST levels in children between Caucasians, East Asians, and South Asians [12], or a statistically significant difference deemed to be not clinically significant in adults between Caucasians (i.e. Italian and Nordic), East Asians (i.e. Chinese), and West Asians (i.e. Turkish) [75]. Ethnic difference in AST levels, therefore, remains inconclusive and requires further investigation. Although Ceriotti et al. found only minor and clinically insignificant ethnic differences in alanine aminotransferase (ALT) levels [75] in East Asians compared to Caucasian and West Asian individuals, many studies reported the presence of ethnic differences in ALT [12,69,76]. For instance, differences were reported between Caucasians and Hispanics as well as between Blacks and Hispanics [69]. An adult study using NHANES data also reported higher ALT and AST activities in Hispanics than Caucasians and Blacks [77]. In children, South Asians and Caucasians have been reported to have higher ALT levels than East Asians [12], and higher values in Caucasians than Blacks [76]. Gamma-glutamyltransferase (GGT) levels have also been found to differ between East Asians, West Asians, and certain Caucasians (i.e. greater upper limit in a Nordic population than Chinese, Turkish, and Italian) [75] and between Blacks and Caucasians (i.e. higher in Blacks) [73]. Certain hepatic markers (e.g. AST and total bilirubin) require further study to gain a better understanding of their ethnic differences.

3.1.3. Cardiac markers

Ethnic differences in levels of numerous cardiac biomarkers, including cardiac troponin I (cTnI), ischemia modified albumin (IMA), and creatine kinase muscle-brain fraction (CK-MB) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), have been studied [78–80]. While NT-proBNP, a diagnostic biomarker of congestive heart failure [81], was reported not to differ between Black and Caucasian adults [78], cTnI, CK-MB and IMA were reported to be higher in Black compared to Caucasian adults [78,79]. However, the investigation by Montagnana et al. of IMA and NT-proBNP [78] studied Caucasian participants who were described as “non-immigrant”, yet this descriptor was not used for the Black participants; this suggests that

Table 2. Available literature evidence for ethnic differences in biomarker levels.

Biomarker/test name (abbreviation)	Ethnic differences[a,b]	References
Routine chemistry markers		
Alanine aminotransferase (ALT)	SA,CA > EA	[12]
	HC > CA > BK	[69,76,77]
Aldosterone	CA > BK	[70]
Amylase	SA,EA > CA	[12]
	BK > Asian > CA	[105]
Apolipoprotein A1 (ApoA1)	BK > CA	[83]
	Japanese > Chinese, SEA[c]	[66]
Apolipoprotein E (ApoE)	BK > CA	[83]
C-reactive protein (CRP)	BK > HC > CA	[103,104]
	SEA, Japanese > Chinese[c]	[65]
Creatine kinase (CK) [including cardiac creatine kinase (CK-MB)]	BK > CA	[25,31,36,79,97,98,100,101]
Creatinine	BK > HC,CA	[71,72]
Cardiac troponin I (cTnI)	BK > CA	[79]
Cystatin C (CysC)	CA > BK,HC	[72]
Ferritin	BK,EA,SEA > CA > SA	[13,108,109]
Gamma-glutamyltransferase (GGT)	BK > CA > EA	[73,75]
	Nordic > Italian, Turkish[c]	[75]
Globulins	Asian, BK > CA	[25,99]
High-density lipoprotein cholesterol (HDL-C)	BK > CA,HC	[82,83,85]
Immunoglobulin E (IgE)	HC > CA	[96]
Immunoglobulin G (IgG)	BK,EA,SA > CA	[12,92–94]
	SEA > EA	[65]
Immunoglobulin M (IgM)	EA,SA > CA	[12]
Iron	CA,HC > BK	[108]
Ischemia modified albumin (IMA)	BK > CA	[78]
Lipoprotein(a)	BK > CA	[83]
Magnesium	CA,EA > SA	[12]
Myoglobin	BK > CA	[102]
Renin	CA > BK	[70]
Total iron binding capacity (TIBC)	HC > BK,CA	[108]
Total protein (TP)	BK > CA	[25,73,99]
	SEA > EA > CA,SA	[12,66]
Transferrin	SA > CA,EA	[12]
Transferrin saturation	CA > HC,BK	[108]
	EA,SEA > CA	[109]
Triglycerides (TG)	CA > BK	[25,82–85]
Vitamin D binding protein (VDBP)	HC,CA > BK	[106,107]
Fertility markers		
Calculated free testosterone	BK,CA > SA	[111]
Follicle stimulating hormone (FSH)	Asian > CA	[112,113]
Sex hormone-binding globulin (SHBG)	BK,CA > SA	[111]
Endocrine markers		
Calcitonin	BK > CA	[126,127]
Free thyroxine (FT4)	CA > BK	[121]
	EA > SA > CA	[13]
Intact PTH (iPTH)	SA > EA,CA	[13]
Leptin	BK,CA,HC > EA	[116–118]
Parathyroid hormone (PTH)	BK > CA	[67,122–124]
	Japanese > Chinese, SEA[c]	[66]
Thyroid stimulating hormone (TSH)	CA > BK	[29,63,119–121]
Total thyroxine (TT4)	HC > BK,CA	[29]
	EA > CA > SA	[13]
Total triiodothyronine (TT3)	CA > EA,SA	[13]
Cancer markers		
Prostate specific antigen (PSA)	BK > CA > EA,SA,WA	[64,128–137]
Hematologic markers		
Erythrocyte protoporphyrin	HC > BK,CA	[108]
Hematocrit (Hct)	CA > Asian, BK	[25,108,146,150]
Hemoglobin (Hb)	CA > Asian, BK	[25,108,146–150]
Mean corpuscular hemoglobin (MCH)	CA > Asian, BK	[25,108,146,149,150]
Mean corpuscular hemoglobin concentration (MCHC)	CA > Asian, BK	[25,108,146,149,150]
Mean corpuscular volume (MCV)	CA > Asian, BK	[25,108,149,150]
Red blood cell distribution width	BK > CA	[108]
White blood cell count (WBC)	CA > BK	[25,108,146,149,150]
Vitamins and carotenoids		
Calcidiol (25-hydroxyvitamin D)	CA > HC,BK	[67,85,122,143,144]
Cobalamin (vitamin B12)	BK > CA	[47,85,139–142]
Folate	CA > BK,HC	[85]
	Chinese, SEA > Japanese[c]	[66]
Lutein and zeaxanthin	BK,HC > CA	[28,85]
Lycopene (including trans-lycopene)	BK > CA > HC	[28,85]
Transcobalamin (TC) I	BK > CA	[141,142]

(*continued*)

Table 2. Continued

Biomarker/test name (abbreviation)	Ethnic differences[a,b]	References
Transcobalamin (TC) II	BK > CA	[141]
Vitamin B6	CA > BK	[85]
Vitamin C	BK,HC > CA	[85]
α-Carotene	HC > CA > BK	[28,85]
β-Cryptoxanthin	BK,HC > CA	[28,85]

BK: Black; CA: Caucasian; EA: East Asian; HC: Hispanic; SA: South Asian; SEA: South East Asian; WA: West Asian.
Results from different studies have been combined, where appropriate, for simplification. Conflicting results and those with unknown direction of ethnic difference (i.e. absence of a *post hoc* test) have not been included in the table. Furthermore, some results are specific for certain age and/or sex groups; see Section 3 for more information.
[a]For biomarkers with numerous findings, ethnic differences have been indicated based on the most commonly noted results.
[b]Commas between ethnic categories indicate ethnicities with either similar values or unknown differences between them.
[c]Differences were reported between subgroups within a defined ethnic group.

place of birth may be a confounding factor in this study. Apple et al.'s investigation of cTnI and CK-MB [79] did not have sufficient statistical power to calculate differences for ethnicities other than Black and Caucasian, because Hispanic and Asian ethnicities comprised only 2% and 5% of participants, respectively. Another study reported no differences in cTnI between adult East Asians, South East Asians, and South Asians [80], although other cardiac biomarkers were not investigated. Given the limited research on the influence of ethnicity on cardiac biomarkers, particularly in children, further investigations are warranted.

3.1.4. Lipids, lipoproteins, and apolipoproteins

Numerous studies have examined the influence of ethnicity on lipids, lipoproteins, and apolipoproteins. Triglyceride (TG) levels have been consistently reported to be lower in Black compared to Caucasian pediatric and adult participants [25,82–85]. Similarly, non-HDL-C levels, a calculated parameter representing atherogenic lipoproteins [86,87], were reported by Gardner et al. to be lower in Black compared to Caucasian adults [88]. On the other hand, Winkleby et al. reported no difference in non-HDL-C levels between Caucasian, Black, and Hispanic pediatric and young adult participants [89]. Although both studies used the same data (i.e. NHANES 1988–1994), Gardner et al. studied samples from subjects $\geq$25 years of age, while Winkleby et al. studied samples from subjects 6–24 years of age. In children, there appears to be some discrepancy in non-HDL-C levels between Blacks and Caucasians. In female children and adolescents, non-HDL-C levels were reported to be higher in Caucasians than Hispanics [61], and in both sexes of children and adolescents, Blacks were reported to have generally lower non-HDL-C levels than Caucasians and Hispanics [61]. On the other hand, Srinivasan et al. found no differences in non-HDL-C levels between Black and Caucasian children and adolescents [90]. Such inconsistency in results for pediatric participants might be because of geographical variation or year of participation, as Srinivasan et al. analyzed data collected between 1992 and 1994 from one city in Louisiana (i.e. Bogalusa) [90], while Dai et al. analyzed more recent NHANES data (2005–2010), which represent the recent general population of the US [61]. These conflicting results suggest that the influence of ethnicity on lipid biomarkers needs to be studied further in new studies that better represent the current US population.

In contrast to TG and non-HDL-C, high-density lipoprotein cholesterol (HDL-C) was found to be higher in Black compared to Caucasian and Hispanic children and adolescents [83,85]. Project HeartBeat! also reported higher levels in Black than non-Black children and adolescents [82]. Differences in HDL-C levels within Asian populations have been investigated by two studies. In adults, differences were reported between East Asians and South East Asians (generally higher in Japanese than Chinese and South East Asians, although pairwise ethnic comparisons were not performed) [65]. Conversely, in newborns, no ethnic difference was reported between South East, East, and South Asians [91]. The latter two studies again highlight the importance of age when studying ethnic differences.

Total cholesterol levels have been reported to be lower in Black compared to Caucasian adults [25], though reports on children and adolescents are inconclusive [83–85]. A review by Srinivasan and Berenson [83] reported that pediatric total cholesterol was generally higher in Blacks compared to Caucasians, but deGroot et al. [84] concluded that their similar pediatric difference was not clinically significant. Conversely, Kant and Graubard found no ethnic pediatric difference between Blacks, Caucasians, and Hispanics [85]. Regional environmental factors (e.g. diet, climate, healthcare, and lifestyle), different pre-analytical and analytical techniques, and the year of participant recruitment could have contributed to the different observations, as deGroot et al. recruited individuals from the state of Ohio before 1977 while Kant et al. analyzed NHANES data gathered from individuals across the country between 2003 and 2006. For findings to be

applicable to an entire country such as the US, it would be best for study participants to be recruited from all areas of the country. Thus, analyzing NHANES data is preferable when assessing ethnic differences in the US.

As reviewed by Srinivasan et al., apolipoprotein A1 (apoA1), apolipoprotein E (apoE), and lipoprotein(a) levels have been found to be lower in Caucasian compared to Black pediatric participants [83]. Saha et al. found no difference in levels of total cholesterol, apoA1, apoA2, or apolipoprotein B (apoB) between South East Asian (i.e. Malay), East Asian (i.e. Chinese), and South Asian (i.e. Indian) newborns [91]. While Ichihara et al. did not find differences in apoB and apoE levels, they reported differences in apoA1 levels between East and South East Asian adult populations, with Japanese having generally higher values than Chinese and South East Asians [66]. Like Saha et al., Chinese and South East Asian values reported by Ichihara et al. were relatively similar. Thus, future studies need to focus on investigating ethnic differences between various specific South, East, and South East Asian populations in children, adolescents, and adults.

3.1.5. Proteins, peptides, and enzymes

Many investigations into ethnic differences for immunoglobulins are reported in the literature. Although adult immunoglobulin M (IgM) levels were found to be similar between Blacks and Caucasians in one study [92], another study found higher adult and pediatric IgM levels in Caucasian compared to Black females, but not males [93]. Higher pediatric IgM levels in Caucasians compared to Blacks were also found by Satoh et al. [94]. Furthermore, Colantonio et al. noted higher pediatric IgM in East Asians and South Asians compared to Caucasians [12]. Combined results of studies indicate pediatric immunoglobulin G (IgG) levels to be higher in East Asians, South Asians, and Blacks compared to Caucasians [12,94]. Other reports on IgG that showed consistent findings were a study of pediatrics and adults [93] and another of adults only [92], with higher IgG levels in Blacks compared to Caucasians. Ichihara et al. found that mean IgG levels in adults were different by region, with relatively higher values in South East Asians compared to Chinese and Japanese, although *post hoc* comparisons were not performed [65]. In contrast to IgG and IgM, pediatric immunoglobulin E (IgE) levels have been found to not differ between South Asian, Caucasian, and Black children born and living in London, England [95]. A study of postnatal women living in the US found Blacks and Hispanics to have higher total IgE values compared to Caucasians [96]. Thus, it is possible that the location of residence and/or age influence ethnic-specific IgE levels. Reports on immunoglobulin A (IgA) are conflicting in both adult and pediatric populations, which may be due to changes in environment, lifestyle or analytical factors over time. While an older study consisting of adults and pediatrics found higher IgA levels for Blacks compared to Caucasians [93], newer studies reported no difference for adult [92] or adolescent [94] IgA levels. Furthermore, IgA levels were not found to differ between Caucasians, East Asians, and South Asians by CALIPER [12]. In general, more investigations on adults and children would improve our understanding of ethnic differences for immunoglobulins.

Investigations into levels of total protein (TP), globulins and CK have consistently noted that Blacks have higher levels than Caucasians [25,31,36,73,97–101]. In a study that considered Asians (i.e. East, South, and South East Asians) as a single group, they were also found to have higher TP and globulin levels compared to Caucasians [25]. More specifically, CALIPER has found ethnic differences in pediatric TP levels, with East Asians having higher values than Caucasians and South Asians [12]. Interestingly, Ichihara et al. also noted ethnic differences in TP within Asian populations, with South East Asians showing generally higher values than East Asians (i.e. Chinese and Japanese) [66]. Myoglobin levels have also been noted to be higher in Black, compared to Caucasian, males but not females [102].

Adult C-reactive protein (CRP) levels have been reported to be higher in Hispanics than Caucasians [103]. Analysis of CRP levels in a cohort of pediatrics and adults found higher levels in Black compared to Caucasian and Hispanic females, with similar levels in the latter two ethnicities [104]. In males, Blacks were found to have higher CRP levels than Caucasians, with Hispanics having intermediate levels [104]. Ichihara et al. have also found differences within and between East Asian and South East Asian adults, with adult Chinese CRP levels being relatively lower than in adults from South East Asia and Japan [65]. When amylase levels were studied in British residents, adult West Indians (i.e. mainly Blacks) and Asians were found to have higher total mean amylase levels compared to Britons (i.e. mainly Caucasians), while West Indians had slightly higher levels than Asians [105]. Similar to adults, pediatric amylase levels were found to be higher in South Asians and East Asians than Caucasians [12], although blacks were not investigated. Finally, vitamin D binding protein (VDBP) levels have been shown to be higher in adult male Caucasians (but only with monoclonal, not polyclonal, enzyme-linked immunosorbent assays) compared to Blacks [106]. Another randomized clinical trial consisting of adolescents with vitamin D deficiency

found that Hispanics have higher levels of VDBP compared to Blacks [107]. Fortunately, many studies have been conducted on the influence of ethnicity on clinically important proteins and peptides. However, as with many biomarkers in this review, there are gaps for Asian populations.

3.1.6. Markers of Anemia

Ethnic differences in levels of several biomarkers of anemia, including Hcy, iron, ferritin, transferrin, total iron binding capacity (TIBC), and transferrin saturation, have been studied. Estrada et al. reported that adult male, but not female, Caucasians had higher Hcy levels (random and fasting) than Blacks, which may be because of a higher frequency of MTHFR enzyme polymorphisms in Caucasians [47]. In contrast, Gerhard et al. reported higher Hcy levels in Black compared to Caucasian women, although this was no longer significant after adjusting for intake of multivitamins and folate-fortified cereal [51]. Similarly, analysis of post-folic acid fortification era data in the US found no significant ethnic differences between Black, Caucasian, and Hispanic adults (except for males >70 years of age) [50]. Black children were reported to have significantly higher Hcy levels than Caucasians and Hispanics prior to [48], but not after [49], universal nutritional folic acid fortification in the US. Thus, at times, advances in healthcare for a population (i.e. folic acid fortification in the US) can alter environmental factors for a population and consequently account for an apparent ethnic difference.

The influence of ethnicity on the levels of iron and iron binding properties has also been studied. Starting in adolescence, iron levels were reported to be higher in Caucasians and Hispanics than Blacks, while TIBC was higher in Hispanics compared to Caucasians and Blacks [108]. In adults, ferritin has been reported to be higher in Blacks (50–59 years of age) [108], East Asians, South East Asians [109], and Pacific Islanders (males only) [109] than Caucasians. Pediatric ferritin levels have been reported to be higher in East Asians than Caucasians, and higher in both of these ethnicities than in South Asians [13]. In contrast to ferritin, higher pediatric transferrin levels were reported in South Asians compared to East Asians and Caucasians [12]. In females, transferrin saturation was found to be higher in Caucasians than Hispanics and Blacks, mainly in adolescence and adulthood (until the age of 60) [108]. Furthermore, in adult females, East and South East Asians had significantly higher levels than Pacific Islanders and Caucasians, whereas in adult males, East and South East Asian values were significantly higher than Caucasians [109]. Further investigations into ethnic differences for transferrin saturation in Asian children are needed.

3.2. Fertility markers

Few studies have examined ethnic differences in fertility markers. Adult Canadian men of Caucasian and South Asian ethnicity were reported to have similar levels of total testosterone (TT) and bioavailable testosterone (BT) [110]. Conversely, a more dated study found both TT and calculated free testosterone levels were lower in South Asian than Caucasian and Black adults living in England [111]. Similar to Canadian adults, CALIPER's Canadian pediatric analysis of testosterone values found no difference between South Asians, East Asians, and Caucasians [14]. Differences in testosterone reports might be due to environmental and lifestyle factors that differ between Canada and the United Kingdom (UK) and age of participants. Pediatric follicle stimulating hormone (FSH) in males and sex hormone-binding globulin (SHBG) in both sexes were reported to differ between Caucasians, East Asians, and South Asians [14], although the specific nature of this difference was not indicated. However, adult male FSH levels were noted to be higher in Asians than Caucasians [112,113]. Heald et al. reported lower adult male SHBG levels in South Asians than Blacks and Caucasians living in England, with similar levels in the latter two ethnic groups [111]. On the other hand, Rohrmann et al. reported higher adult male SHBG levels in Blacks than Caucasians living in the US [114]. Reports on adult male SHBG levels are conflicting, which may be due to environmental and lifestyle differences between the UK and the US. It has also been reported that SHBG levels may be directly and indirectly correlated with insulin sensitivity and insulin resistance, respectively [111,115]. These correlations may explain some of the observed ethnic differences [111]. Additionally, CALIPER found several other pediatric fertility hormone levels (i.e. estradiol, progesterone, luteinizing hormone, and prolactin) to not differ in males or females between Caucasians, East Asians, and South Asians [14]. Overall, further studies are warranted to determine conclusively the effect of ethnicity on fertility markers.

3.3. Endocrine markers

Reports on ethnic differences in leptin levels are somewhat conflicting. Chen et al. found leptin levels to be lower in East Asian adults compared to Caucasians; however, this difference was significant only in overweight and obese individuals [116]. An adult study by Wu et al. reported that Blacks had the highest, and East

Asians the lowest, levels of leptin, with intermediate levels in Caucasians and Hispanics [117]. In contrast to adults, Danadian et al. found no difference in pediatric leptin levels between Caucasians and Blacks [118]. These findings highlight the importance of considering participant age and BMI when studying ethnic differences in leptin levels.

Certain thyroid hormone levels also differ between ethnic groups: TSH levels have been found to be higher in adolescent and adult Caucasians compared to Blacks [29,63,119–121]. A study of adolescents and adults found higher total thyroxine (TT4) levels in Hispanics than Blacks and Caucasians, with relatively similar levels in the latter two ethnicities [29]. CALIPER also found ethnic differences in pediatric thyroid hormone levels [13]; TT4 levels were highest in East Asians, lowest in South Asians, and intermediate in Caucasians. Free thyroxine (FT4) was found to be higher in adult Caucasians than Blacks [121]. CALIPER found higher FT4 levels in East Asians and lower levels in Caucasians compared to South Asians as well as higher total triiodothyronine (TT3) levels in Caucasians compared to South Asians and East Asians [13].

Numerous studies have reported that Blacks have higher PTH levels than Caucasians in adolescents and adults [67,122–124]. Interestingly, Blacks have been reported to have skeletal resistance to PTH [125], which may be a compensatory mechanism for their greater PTH levels. Ichihara et al. found that Japanese have relatively greater PTH levels than Chinese and South East Asian adults [66]. Furthermore, CALIPER reported higher intact PTH (iPTH) levels in South Asian compared to East Asian and Caucasian children and adolescents [13]. Similar to the ethnic differences in PTH, calcitonin levels have been shown to be higher in Blacks compared to Caucasians [126,127]. Overall, levels of many hormones related to bone and thyroid health are influenced by ethnicity.

3.4. Cancer markers

PSA is one of the most common tumor biomarkers investigated for ethnic differences [64,128–137]. Collective results from numerous PSA studies suggest that Blacks have higher PSA levels than Caucasians, and these groups both have higher PSA levels compared to West Asian, South Asian, and East Asian populations [64,128–137]. Interestingly, higher PSA levels in Blacks appear to parallel a higher prostate cancer prevalence in Blacks compared to Caucasians [128]. Findings of PSA levels within Asian groups [129,130] are rather contradictory. He et al. reported Chinese adults having lower PSA levels than Black, Caucasian, and other East Asian men [137], and Gupta et al.'s study of adult men indicated that South Asians (i.e. Indians) generally had lower PSA levels than Black, Caucasian, East Asian, South East Asian, and West Asian ethnic groups [129]. Differences between and within Asian groups may be due to environmental factors because Chinese living in China have been reported to have lower PSA levels than Chinese living in Taiwan [134]. In addition, prostate volume may affect PSA levels as it has been shown that Caucasians generally have both higher PSA levels and prostate volume than Asians (including South Asian, East Asian, and South East Asian) and West Asians [130,136,138]. Although differences in PSA levels have been demonstrated between Blacks and Caucasians, more studies are required to clearly establish the influence of ethnicity on its levels in Asian populations. Furthermore, the influence of ethnicity on other cancer biomarkers needs to be studied.

3.5. Vitamins and carotenoids

Ethnic differences in levels of vitamins and carotenoids have also been analyzed by numerous studies. Kant and Graubard reported that pediatric levels of vitamin A, vitamin B6, vitamin E, and α-carotene were lower in Blacks compared to Caucasians and trans-lycopene levels were higher in Blacks compared to Hispanics and Caucasians [85]. This study also found that vitamin C, β-cryptoxanthin, lutein, and zeaxanthin levels were higher in Blacks and Hispanics compared to Caucasians. Similarly, Ford et al. found lower pediatric levels of α-carotene and higher levels of lycopene, β-cryptoxanthin, lutein, and zeaxanthin in Blacks compared to Caucasians [28]. Hispanics were also found to have significantly higher pediatric α-carotene, β-cryptoxanthin lutein, and zeaxanthin and lower lycopene levels than Caucasians. β-Carotene levels were found by both Ford et al. and Kant et al. to not differ between Caucasians, Blacks, and Hispanics. In contrast to the study by Kant et al., CALIPER found no significant ethnic difference for vitamins A and E in the ethnically diverse Canadian pediatric population [18]. Conflicting results in ethnic differences for vitamin A and E may be due to environmental factors, as vitamin A levels have been suggested to be affected more by vitamin supplement use and SES compared to genetic factors [42]. Folate levels have been reported to be different between adult Asian ethnic groups, with Japanese values relatively lower than Chinese and South East Asians [66]. On the other hand, CALIPER found pediatric folate levels to not differ between Caucasians, East Asians, and South Asians [13]. Furthermore, pediatric folate levels have been reported to be lower in Blacks and Hispanics compared to

Caucasians [85]. Strong evidence suggests that cobalamin levels are higher in Blacks compared to Caucasians [47,85,139–142]. Furthermore, CALIPER reported that during the pediatric years, there was a trend toward higher cobalamin levels in East Asians compared to Caucasians and South Asians, though this difference did not reach statistical significance [13]. Transcobalamin (TC) I and TC II have also been reported to be higher in Blacks compared to Caucasians [141,142]. More studies to investigate ethnic differences in adult levels of vitamins and carotenoids, while considering diet and other environmental factors, are needed.

Several studies have shown that calcidiol is significantly higher in Caucasians compared to Hispanics or Blacks [67,85,122,143,144] in pediatrics and adults, while one study noted a trend to this effect that did not reach statistical significance [145]. In addition, CALIPER has reported East Asians having lower calcidiol levels compared to Caucasians and South Asians, but these differences did not reach statistical significance [13]. On the other hand, ethnic difference in calcitriol (1,25-dihydroxyvitamin D) levels seems to be inconclusive, possibly because of age and sex differences between studies [67,122,145]. Calcitriol levels were reported to be higher in Black compared to Caucasian postmenopausal women (55–75 years of age) [122], while no such ethnic difference was reported for premenopausal women [145]. Another study found a trend toward higher adult calcitriol levels in Blacks than Caucasians, though this difference did not reach significance [67], possibly because premenopausal and postmenopausal women, as well as men, were included in this study. Thus, the influence of ethnicity on calcidiol (comparison of Asian populations to Caucasians and Blacks) and calcitriol levels need further research, preferably with separate analysis for sex and menopausal state.

3.6. Hematological markers

Several studies have reported ethnic differences in hematological markers. It is a common finding that levels of most hematologic markers, including hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and white blood cell count (WBC), are lower in Blacks compared to Caucasians, [25,108,146–150]. Similarly, Asians (i.e. East, South, and South East Asians) were found to have lower Hb, Hct, MCV, MCH, and MCHC than Caucasians [25]. On the other hand, median red blood cell distribution width was reported to be higher in Blacks compared to Caucasians, and erythrocyte protoporphyrin levels were found to be higher in Hispanics compared to Caucasians and Blacks [108]. Ethnic differences in platelet counts in the literature are conflicting. In an analysis of adult and pediatric US data, it was found that, below the age of 50, Black females had higher platelet counts than Caucasian females [108]. Similarly, Humberg et al. demonstrated a higher upper limit for platelet counts in Black (i.e. Gabonese) compared to Caucasian infants (4–9 weeks old) and children (18–60 months old), and particularly in infants [146]; however, this study also discussed other reports that found lower platelet counts in different African populations, suggesting the possibility that higher platelet counts in Blacks may be specific to some African populations, such as Gabonese. Another study suggested that higher platelet counts in Blacks were specific to adolescents (12–17 years of age) and this ethnic difference was not observed in children (5–11 years of age) [150]. While differences in most hematological markers between Caucasians and Blacks are consistent between many studies, no definite agreement exists regarding the influence of ethnicity on platelet levels; thus, further studies are warranted.

4. Conclusions and future directions

Numerous studies have reported differences in biomarker concentrations between major ethnic groups. However, in many cases, results are conflicting, and the clinical significance of ethnic differences observed in biomarker concentration is unclear. The results from various studies, which are summarized in Table 2, are divided into six categories of biomarkers. Overall, several routine chemistry markers have been examined for ethnic differences, while very few cancer biomarkers have been investigated.

Consistent ethnic differences for a relatively limited number of biomarkers, including differences in Hb, calcidiol, and PSA levels between Blacks and Caucasians, have been reported in the literature. Despite these findings, it is vital to study the underlying causes of such ethnic differences to gain a better understanding of their clinical applicability. One important consideration is to determine whether these differences represent ethnic-specific susceptibility to diseases. While PSA, as an example, has been shown to be relatively higher in Blacks [128,132,133], Blacks have also been reported to have a higher prevalence of prostate cancer [128]. Thus, it may be advisable to not treat higher levels of such biomarkers as healthy in certain ethnic groups. On the other hand, Blacks have been reported to have lower calcidiol [67,85,122,143,144] and higher PTH [67,122–125] levels compared to Caucasians, yet Blacks have relatively higher bone mineral density and lower

risk of bone fractures than Caucasians [151–153]. In fact, several physiological features have been suggested to compensate for ethnic differences in PTH and calcidiol levels in Blacks [124,125,143,153]. Therefore, the influence of ethnicity on serum calcidiol levels should be considered in clinical settings. Furthermore, for biochemical markers with sufficient and consistent literature findings on their ethnic differences, local laboratory studies are warranted to verify these ethnic differences in the region of interest prior to using this information for clinical interpretation of laboratory tests.

Conversely, several biomarkers exhibit inconsistent findings regarding ethnic differences, as shown in Table 2. These differences between studies may be because of methodological differences, including differences in region of residence, sample collection year, and statistical methods. Another source of inconsistency in results stems from differences in environmental factors that influence individuals of different studies. As previously discussed, cardiac and lipid biomarkers are examples of biomarkers that are significantly influenced by environmental factors, which suggests the importance of considering various environmental factors such as diet. Conflicting results between studies may also be because of differences in age and sex of participants. Endocrine marker and vitamin levels are examples of biomarkers requiring attention to participant age and/or sex. It is, therefore, important for future studies to evaluate the influence of ethnicity on biomarkers with inconclusive findings while taking into consideration the specific demographics of the population of interest.

In general, there is ample evidence regarding biomarker levels in Caucasians and Blacks; however, additional studies are required to analyze other ethnicities. For examples, more studies in Asian subjects are required to examine ethnic differences in the levels of lipids, proteins, and cancer biomarkers. Additionally, in multi-ethnic countries (e.g. Canada and the US), studies identifying differences between all present ethnicities is lacking. For instance, while Canadian studies have compared Caucasians with South Asians and East Asians, more studies are required to compare these ethnicities to Blacks, Hispanics, and West Asians. Furthermore, comparison of Blacks, Caucasians, and Hispanics is a common theme across US studies, though additional studies are required to compare these ethnicities to Asian (i.e. East, South, South East, and West Asian) ethnicities. Lack of such studies partially stems from the difficulty in obtaining a sufficient number of samples from these ethnic groups.

Additionally, age categories of study participants have been indicated in Section 3 to identify ethnic differences specifically for pediatric and/or adult groups. This has allowed us to identify age-specific gaps in studies analyzing ethnic differences. For instance, additional pediatric studies are required to identify ethnic differences in levels of cardiac, lipid, and renal biomarkers as well as electrolytes and proteins. Additional adult studies are required to analyze ethnic differences in levels of lipid and renal biomarkers, proteins, vitamins, and carotenoids.

Another limitation of the reported studies is their ethnic categorization. In many cases, research participants who self-identified as belonging to one of the ethnic categories described in Table 1 are not from a single ethnic background. In reality, the majority of individuals are of mixed ethnic backgrounds. Such information is also mainly self-reported. Although these factors may reduce the homogeneity of the ethnic-specific reference populations, these remain as the only practical options for obtaining demographic information. For instance, obtaining more exact details by various techniques such as genetic testing is costly and not practical for a routine clinical setting. Thus, we recommend that future studies include an additional category comprised of individuals of mixed ethnic backgrounds as well as more well-defined ethnic categories (e.g. by obtaining both maternal and paternal ethnic backgrounds).

In summary, while many ethnic differences have been reported in the literature, it is essential to consider these results in conjunction with the specific demographics of participants and environmental factors that may have contributed to the results, prior to their application in clinical settings. Future studies should focus on analyzing ethnic differences by concentrating on age- and ethnic-specific gaps in the literature. These findings will be essential to establish ethnic-specific RIs, which in turn will allow more accurate interpretation of laboratory test results and clinical decision-making.

Disclosure statement

No potential conflict of interest was reported by the authors.

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