Irish Journal of Medical Science (1971 -) (2019) 188:249–258
https://doi.org/10.1007/s11845-018-1825-y

ORIGINAL ARTICLE

Variations in biochemical values for common laboratory tests: a comparison among multi-ethnic Israeli women cohort

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Received: 10 March 2018 / Accepted: 19 April 2018 / Published online: 28 April 2018

Abstract

Background Biochemical laboratory values are an essential tool in medical diagnosis, treatment, and follow-up; however, they are known to vary between populations. Establishment of ethnicity-adjusted reference values is recommended by health organizations.
Aim To investigate the ethnicity element in biochemical lab values studying women of different ethnic groups.
Methods Biochemical lab values ($n = 27$) of 503 adult Israeli women of three ethnicities (Jewish Ashkenazi, Jewish Sephardic, and Bedouin Arab) attending a single medical center were analyzed. Biochemical data were extracted from medical center records. Ethnic differences of laboratory biochemicals were studied using ANCOVA to analyze the center of the distribution as well as quartile regression analysis to analyze the upper and lower limits, both done with an adjustment for age.
Results Significant ethnic differences were found in almost half ($n = 12$) of the biochemical laboratory tests. Ashkenazi Jews exhibited significantly higher mean values compared to Bedouins in most of the biochemical tests, including albumin, alkaline phosphatase, calcium, cholesterol, cholesterol LDL and HDL, cholesterol LDL calc., folic acid, globulin, and iron saturation, while the Bedouins exhibited the highest mean values in the creatinine and triglycerides. For most of these tests, Sephardic Jews exhibited biochemical mean levels in between the two other groups. Compared to Ashkenazi Jews, Sephardic Jews had a significant shift to lower values in cholesterol LDL.
Conclusions Ethnic subpopulations have distinct distributions in biochemical laboratory test values, which should be taken into consideration in medical practice enabling precision medicine.

Keywords Biochemical tests · Ethnicity · HER - electronic health records · RI - reference intervals

Introduction

Clinical biochemical analyses are routinely done as part of the baseline phenotype determination in medical diagnosis, treatment, and follow-up. The guidelines of the International Federation of Clinical Chemistry (IFCC) recommend that every country should establish reference intervals (RIs), taking into account sex, age, and ethnicity [1–4]. In general, although ethnic background is acknowledged as a factor in biochemical RI values, many of the diagnostic laboratories worldwide follow the RIs as they appear in the scientific/professional literature, or implement reference values from Western, mainly Caucasian, cohorts, which are not necessarily commensurate with those of local ethnic groups.

Several studies have demonstrated racial/ethnic differences in RIs of various laboratory tests with the majority focusing on Caucasian compared to Afro-American origins. For example, compared with Caucasians, Afro-Americans show significantly lower thyrotropin, total white blood cell (WBC), neutrophil counts, platelet counts, hematocrit, MCH, MCHC, and hemoglobin [5–7].

Additionally, studies in different world regions, including southern Ghana, Kenya, southern and eastern Africa, Saudi Arabia, Turkey, Pakistan, and China [8–17], have also found significant changes in hematological and biochemical values compared with currently used reference ranges. For instance, red blood cell parameters (hemoglobin, hematocrit, and RBC counts) were lower in Ghana (Kintampo area) compared to the standard values for Caucasians (USA) [8] Similarly, biochemical analyses done in

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different countries demonstrated far lower blood levels for various tests in comparison to western industrialized countries [8–17].

Ethnic diversity is of special importance in immigration-based societies. For instance, by 2020, ethnic minorities in the USA will constitute ~35% of the population [17]. Recognizing the importance of these ethnicity changes, the National Health and Nutrition Examination Survey (NHANES) updated in 2011–2012, for the first time, ethnic background of Asian [17]. Thus, as indicated using RI not adjusted to ethnicity might have potential medical and health implications. Furthermore, the genetics and technological revolutions of the past decade have further highlighted the recognition that gaining better insights into human diversity, including ethnicity, is beneficial in improving health and to treat disease. Establishing this goal gave rise to the Obama precision medicine initiative (PMI), which takes into account, among many other factors, ethnicity and race as a factor for better health and medical outcome [18]. The era of big data in health care advances the research and implementation of precision medicine. Utilization of electronic health records (HER), which are comprised of patient personal information such as demographics, ethnicity, medications, laboratory test results, diagnosis, and disease prognosis, can (under adequate privacy limitations) serve as a mining tool and lead to improvement in patient healthcare management [19].

Israel is a multi-ethnic country. However, to the best of our knowledge, there are no studies comparing common laboratory tests across its ethnic groups. According to the Israeli Central Bureau of Statistics, the Israeli population is composed of two main groups: 80% Jews and 20% Arabs (2016 data), [20]. Arabs (Muslims including Bedouins, Christians, and Druze) are the largest minority group in Israel. The Jewish population is comprised of Ashkenazi Jews originating from Europe and Sephardic Jews—of Mediterranean/Middle-Eastern origins. Initially, due to cultural, socioeconomic, and ethnic factors, the main groups exhibited gaps in disease risks and health. However, in recent years, these populations undergo epidemiological transition. Despite improvements in various health indicators in the last 30 years, chronic disease morbidity and mortality rate differences are still found between the Israeli Jewish and Arab populations. For instance, in the early 2000s, coronary heart disease mortality rates of Arab men and women were 1.6 and 2.4 times higher than those of Jewish men and women and diabetes mortality rates were 2.3 and 3.4 times higher, respectively [21].

The aim of this study was to investigate ethnic differences in biochemical lab values in various ethnic groups of Israeli women.

Methods

Data collection

In a retrospective cohort study, women ages 18–52 years, attending a single fertility clinic from August 2004 through August 2010, were identified from existing databases of Soroka Medical Center, the Beer-Sheva district hospital in southern Israel. Clinical and biochemical data, collected from hospital database, included demographic data, diagnostic data, and biochemistry laboratory records for each patient. All attempts were made to ensure the quality of data with all medical and electronic records accessed. The study was approved by the local institutional ethics committee in accordance with the principles of the Declaration of Helsinki.

Biochemical tests

All tests were done at the hospital routine biochemistry laboratory using standard assays. Practically all blood tests were done mornings after minimum 8 h fasting. Specifically, lipid profile was measured using calorimetric reactions and homocysteine and folic acid level measurements were determined using chemiluminescence/immunoassay assays. All diagnoses were classified according to the International Classification of Diseases, 9th Revision.

Ethnicity groups

One of the demographic variables in the dataset was the country of origin of the patient and of both parents. According to Tse and You [22], demographic information in EHR has high level of accuracy and hence could be used to derive ethnicity. All patients were divided into ethnic groups according to the country in which their parents were born. The groups were Ashkenazi and Sephardic Jews and Bedouin Arabs. In cases in which there was no information regarding both parents, we used the more relaxed criterion described in Maayan et al. [23] in which the origin of only one parent is used when the other parent was born in Israel or unknown. In cases where the origin of both parents was missing, the country in which the individual was born was used to determine his origin [24].

Ashkenazi origin included Europe (including the Baltic States and other eastern European countries with the exception of Bulgaria), the former Soviet Union (not including Central Asian countries), the Americas, Australia, and South Africa. Sephardic origin included North Africa including countries in the Middle East, Turkey, Central Asian countries, and Bulgaria. Bedouin origin was derived from the residential Bedouin Local Council.

The remainder of patients who could not be assigned to one of these origins, due to missing values of country of origin, or non-informative counties regarding ethnicity such as Israel, were excluded from this study.

Statistical analysis

All statistical analysis was done using JMP 13 pro (SAS Institute, Cary, NC).

Determining the value of biochemical parameters for each individual, the value for each individual for each biochemical test was based on several measurements that were taken at different occasions in which the patient came to the hospital. Using biochemical data spanning over a duration of several years could potentially be problematic due to errors related to differences in patients' medical state at time of blood test, technical issues, lab errors, etc. Except for the patients' medical state, all of these errors are random errors which affect all patients, no matter what ethnic group they belong to and relate to the dependent variable (aka the outcome (*Y*) variable). In a statistic model, having a dependent variable with a big error term adds extra noise which in turn lowers the analysis power to detect a true effect [25]. Hence, all the *p* values obtained under such conditions are expected to be under-estimated: thus, under this limitation, obtaining a significant result is a strong indication that this result is a true result. On the other hand, the patient medical state error could be divided into two sources, one is a temporary change which adds to the random error discussed above and the second is a true change that affects the biochemical blood count and hence should be accounted for in the analysis. We used two statistical approaches to minimize such errors: first, we used the median value, which is not influenced by extreme values, and hence less vulnerable to outliers; secondly, we repeated the same statistical analysis using also the mean values (instead of the median) for each individual. Through this approach, results found to be significant twice, using both mean and median values, indicated that the probability of the result accuracy was high (despite possible "noise" created if data potentially did not represent correctly each individual). In addition, in order to minimize outlier values that could be the cause of the significant result, all analyses, where outliers were identified (using distribution histogram output of the software for each biochemical parameter), were repeated yet once more, this time excluding the outliers. If the results were still significant after excluding the outliers, the original results before exclusion are reported. In those cases where the exclusion of outliers transformed the results to become non-significant, the new results after exclusion are reported.

Statistical models

In order to test the effect of ethnicity on the different biochemical parameters, we used regression model on three parts of the distribution, namely, the center and the upper and lower limits.

For testing the effect of ethnicity on the center of the distribution of each biochemical test, an ANCOVA test was conducted with adjustment for age (as the covariate). The parameter estimate of each ethnicity allowed us to assess whether the mean values of the different ethnic groups played a role in determining biochemical test values.

Reference intervals were defined as 2.5th and 97.5th percentiles for the lower and upper limits of the range, respectively. Quantile regression models were conducted for the lower and upper limit of the range for each laboratory test comparing across racial/ethnic groups. Quantile regression is a statistical method which is pretty robust to statistical outliers and yields much more information about the underlying associations [26], since it avoids parametric assumptions about the error distribution. The standard error for each parameter was estimated running 1000 bootstrap samples. Adjustment for age was applied, and the estimator was included in the report only in those cases where the adjustment was significant; otherwise, the estimates of the model without the age adjustments were reported.

Results

General characteristics of the study cohort

The study cohort included 503 adult women aged 18–52 years. The ethnicity distribution was 54% Jewish Sephardic, 23% Jewish Ashkenazi, and 23% Arab Bedouin. The mean and median biochemical values of the general cohort are summarized in Table 1. For comparison, the RIs are also included.

Ethnic differences in mean biochemical values

The mean biochemical values of the different ethnic groups are summarized in Table 2.

Table 3 summarizes results obtained from an ANCOVA analysis, where the origin was the main effect and age was entered as a covariate. Significant racial/ethnic differences in average values were found in 12 of the 27 laboratory tests analyzed, including albumin, alkaline phosphatase, calcium, cholesterol, cholesterol LDL and HDL, LDL calc., creatinine, folic acid, globulin, iron saturation, and triglycerides. Two more biochemical parameters, namely, transferrin and VLDL, showed a significant main effect of origin, but the post hoc test (Tukey) to determine which origins differed did not reveal any significant differences between the groups. Among the significant results, in 5 biochemical tests, the mean values for Ashkenazi Jews were significantly higher than the mean values of Bedouins, whereas Sephardic Jewish mean values were in-between; hence, it did not differ significantly from either of the other two groups. These included albumin, alkaline phosphatase, calcium, cholesterol HDL, and cholesterol LDL; For four biochemical parameters, the mean values in Ashkenazi Jews were higher than both Bedouins and Sephardic Jews, including cholesterol, LDL calc., folic acid, and iron saturation; it is of interest that mean cholesterol LDL values of Ashkenazi Jews were significantly higher than those of Sephardic Jews, whereas Bedouins mean values were in-

Table 1 The general characteristics of blood biochemical and lipid values of the study population cohort

Lab test	*N*	Mean	Std Dev	Median	Range	Reference
Albumin g/L	474	39.1	04.2	40	23–48	35–52
Alk. phosphatase (U/L)	483	82.22	37.68	73.2	31–481	0–98
Amylase (U/L)	212	67.59	37.4	61.75	22.75–323.19	0–55
Bilirubin total (μmol/L)	486	9.41	4.1	9.4	3.76–44.13	5–21
Calcium (mmol/L)	472	2.29	0.11	2.31	1.87–2.73	1.8–2.8
Cholesterol (mmol/L)	453	4.72	0.83	4.67	2.44–8.31	2.59–5.70
Cholesterol HDL (mmol/L)	434	0.9	0.26	0.84	0.4–2	0.91–2.07
Cholesterol LDL (mmol/L)	245	2.72	0.79	2.62	1.11–6.50	0–3.37
Cholesterol LDL calc.*	416	106.08	25.91	104.88	33.50–192	
Creatinine (μmol/L)	490	55.69	9.72	55.69	30.94–136.14	5.03–106
Folic acid (nmol/L)	215	22.55	9.18	20.85	4.83–52.80	7–45
Globulin (g/L)	460	31	3.2	30.7	22–47	23–37
Glucose (nmol/L)	491	4.89	0.97	4.70	3.33–13.96	2.22–6.38
GOT (AST) (μkat/L)	488	0.386	0.3977	0.31	0.1833–5.8112	0–1.617
GPT (ALT) (μkat/L)	488	0.36	0.55	0.26	0.08–9.39	0–56 0–0.94
Homocystein (μmol/l)	246	8.86	6.45	7.75	3.20–85	4–17
IRON (μmol/L)	274	12.39	5.59	12.04	1.97–44.75	11.63–31.3
Iron saturation	56	0.216	0.1002	0.020	0.04–0.48	0.20–0.50
Lipase (μkat/L)	79	0.74	1.26	0.47	0.2–10.43	0–60 0–1
Phosphorus (mmol/L)	450	1.17	0.14	1.18	0.68–1.68	0.81–3.07
Protein total (g/L)	477	69;9	05.7	70.7	46.6–88	46–87
Transferrin (μmol/L)	233	36.4	6.93	35.3	22.75–74.5	
Triglycerides (mmol/L)	452	1.28	0.64	1.11	28.00–384.75 0.32–4.35	0–2.2
Urea (mmol/L)	490	8	2.07	7.8	2.54–16.48	0–18
Uric acid (μmol/L)	478	243.3	58.30	236.16	101.12–473.50	137–393
Vitamin B12 (pmol/L)	260	275.13	90.47	255.93	118.49–576.41	99.60–672.14
VLDL (mmol/L)	411	0.55	0.25	0.49	0.16–1.53	0–1.04

*LDL calculated

between, not differing significantly from either other two groups. Bedouins differed from both Ashkenazi and Sephardic Jews in mean creatinine values; average values of triglycerides differed significantly between Bedouins and Sephardic Jews but not from Ashkenazi Jews.

We also analyzed the interaction of age with ethnic group, testing whether age influenced the biochemical values differently in the different ethnicities. Only two biochemical parameters showed significant results for the interaction, namely, glucose and urea (data not shown). For urea, the main effect of ethnic groups was not significant and for glucose, although the main effect of ethnicity did come out significant, after removing the outliers, this significance was lost. Additional analysis was done to strengthen the reliability of the results presented in Table 3 (see details in the Methods section). The first, using the mean value as the representative of each individual for each biochemical test resulted in similar results to those using the median except for bilirubin total and iron, which were not significant in this new analysis. The second, repeating the original analysis after excluding the outliers, generated similar results except for differences in glucose and iron which were not significant in this new analysis.

Ranges of biochemical laboratory tests by ethnicity

Both lower and upper limits of normal ranges for the 27 biochemical laboratory tests, stratified by ethnicity (Ashkenazi and Sephardi Jews and Bedouin Arab), are summarized in Table 4 for lower limits and Table 5 for the upper limits. As shown in Table 2, there were differences between the different ethnic groups in terms of the range of biochemical values, expressed in the lower and upper values. To assess whether these differences in the normal range were statistically significant, quantile regressions were conducted using ethnicity and age as independent variables. The analyses were done also with mean values as representing each individual (as opposed to the median values, see Methods for details) to verify significance. For lipase and iron saturation, the data that was available was for less than 80

Table 2 The general characteristics of mean blood biochemical values for each ethnic group

	Ashkenazi			Bedouin			Sephardic		
Lab test	*N*	Mean (SD)	Range	*N*	Mean (SD)	Range	*N*	Mean (SD)	Range
Albumin	108	40.0 (0.6)	27.3–48.0	111	3.78 (0.43)	23–47	255	39.3 (0.42)	23.4–48
Alk. phos	111	76.92 (31.04)	31–268.67	113	90.24 (36.7)	41–297.60	259	80.99 (40.2)	36–481
Amylase	58	63.1 (34.69)	30–291	34	68.3 (49.28)	28–323.19	120	69.56 (34.89)	22.75–302
Bili total	111	10.09 (5.64)	4.79–44.13	114	8.89 (3.25)	0.24–1.33 4.10–22.75	261	9.41 (3.42)	3.76–27.88
Calcium	109	2.31 (0.10)	2.07–2.73	110	2.27 (0.10)	2.02–2.61	253	2.29 (0.12)	1.87–2.59
Cholest	106	5.03 (29.83)	3.26–7.16	102	4.42 (0.78)	2.44–6.79	245	4.71 (0.83)	2.69–8.31
HDL	99	0.94 (0.26)	0.57–1.81	96	0.85 (0.24)	0.40–1.66	239	0.90 (0.26)	0.43–2.00
Cholest LDL	58	2.98 (0.91)	1.26–6.50	40	2.54 (0.70)	1.52–4.22	147	2.66 (0.74)	1.11–4.66
LDL calc.	97	113.46 (26.24)	62–181	93	99.55 (22.78)	33.50–153.43	226	105.6 (26.28)	46–192
Creatinine	112	59.23 (8.84)	34.48–93.70	114	49.50 (7.07)	33.59–66.30	264	56.58 (10.61)	30.94–136.14
Folic acid	47	25.97 (9.36)	7.70–49.63	54	20.71 (8.47)	7.70–43.73	114	22.00 (9.13)	4.83–52.80
Globulin	106	30.2 (3.0)	22–37.8	105	31.7 (3.4)	23–43.8	249	31.1 (3.2)	23.3–47
Glucose	112	4.95 (0.77)	3.47–7.96	115	5.09 (1.50)	3.64–13.96	264	4.78 (0.71)	3.33–8.44
GOT (AST)	112	0.43 (0.58)	0.18–5.82	114	0.40 (0.44)	0.19–4.70	262	0.36 (0.27)	0.19–2.97
GPT (ALT)	112	0.45 (0.91)	0.08–9.39	114	0.33 (0.37)	0.08–3.45	262	0.34 (0.38)	0.08–3.80
Homocys	51	69.24 (33.36)	30.33–206.38	50	59.18 (26.26)	23.67–185.66	145	66.43 (56.88)	29.59–628.75
Iron	64	13.68 (5.42)	2.98–25.06	49	11.37 (4.81)	3.22–22.06	161	12.19 (5.70)	1.97–44.75
Iron sat	19	.2634 (0.10)	0.11–0.48	5	0.1220 (0.0763)	0.04–0.22	32	0.2026 (0.09.1)	0.04–0.45
Lipase	27	0.51 (0.24)	0.20–1.19	15	1.05 (2.60)	0.23–10.43	37	0.79 (0.84)	0.22–4.66
Phospho	105	1.17 (0.13)	0.85–1.53	104	1.18 (0.15)	0.74–1.68	241	1.18 (0.14)	0.68–1.58
Prot total	109	69.90 (5.40)	50.30–80.00	112	69.4 (6.4)	49–88	256	70.2 (5.6)	46.6–85
Transferrin	62	35.74 (6.14)	26.45–61.01	35	39.06 (6.62)	25.28–58.06	136	35.99 (7.23)	22.75–74.54
Triglycerides	106	1.35 (0.62)	0.58–3.29	102	1.36 (0.65)	0.32–4.13	244	1.23 (0.64)	0.33–4.35
Urea	112	8.42 (1.89)	3.57–13.77	114	7.56 (1.92)	4.21–12.76	264	8.01 (2.18)	2.54–16.48
Uric acid	110	245.08 (54.73)	129.08–443.16	112	248.05 (55.92)	130.87–407.47	256	240.32 (60.67)	101.12–473.50
Vitamin B12	58	275.94 (80.78)	125.92–576.41	59	272.03 (96.49)	131.55–517.94	143	276.08 (92.20)	118.49–548.61
VLDL	96	0.58 (0.28)	0.23–1.53	88	0.57 (0.25)	0.16–1.26	227	0.53 (0.24)	0.16–1.42

individuals for all ethnic groups together; these are not sufficient numbers when dealing with quartiles on the limit, hence those results are not presented. Table 4 contains the results of the quartile regression of the lower limits (see details in Methods). It includes the *p* values of the main effects of origin alone (when age was not significant); when age was significant, it was included in the analysis and the *p* value of both age and origin are given. Also included are the mean values for the different origins, and in cases that age effect was significant, this is an adjusted mean. The only biochemical parameter that had a significant origin result in both the median and the mean-based analysis, was folic acid: Bedouins differed significantly from Sephardic Jews but both these origins did not differ significantly from Ashkenazi Jews. Alkaline phosphates, bilirubin total, and vitamin B12 turned out significant in the median-based analysis but not in the mean-based analysis. On the other hand, ethnic differences in levels of cholesterol, cholesterol HDL, cholesterol LDL calc., and creatinine turned out significant in the mean-based analysis but not in the median-based analysis.

Table 5, similar to Table 4, describes the results for the upper limit, in which three biochemical parameters were significant for origin effect in both median- and mean-based analysis. In cholesterol, LDL calc., and creatinine, the Ashkenazi Jews differed significantly from both Bedouin and Sephardic Jews who did not differ significantly from each other. In glucose, the Bedouins differed significantly from Sephardic Jews but both these origins did not differ significantly from Ashkenazi Jews. In addition, ethnic differences in cholesterol HDL, GOT, GPT, and iron turned out significant in the median-based analysis but not in the mean-based analysis. On the other hand, globulin turned out significant in the mean-based analysis but not in the median-based analysis.

Discussion

The International Federation of Clinical Chemistry and precision medicine initiation identified and recommended exploring and

Table 3 Effect of ethnicity on biochemical median values adjusted for age

	Age	Origin	Ashkenazi	Bedouin	Sephardi
Albumin	0.011*	0.005**	40.2^{A}	38.2^{B}	39.2^{AB}
Alk. phosphatase		0.039*	72.39^{A}	85.07^{B}	77.50^{AB}
Amylase		0.466	62.55^{A}	63.59^{A}	68.69^{A}
Bilirubin total		0.046*	9.92^{A}	8.55^{B}	9.07^{AB}
Calcium		0.037*	2.31^{A}	2.28^{B}	2.30^{AB}
Cholesterol	0.000***	0.000***	4.93^{A}	4.47^{B}	4.65^{B}
Cholesterol HDL		0.045*	1.15^{A}	1.03^{B}	1.11^{AB}
Cholesterol LDL	0.000***	0.015*	2.96^{A}	2.63^{AB}	2.63^{B}
Cholesterol LDL calc.	0.000***	0.008**	112.33^{A}	101.01^{B}	104.37^{B}
Creatinine	0.000***	0.000***	57.46^{A}	50.39^{B}	55.69^{A}
Folic acid		0.012*	25.79^{A}	20.55^{B}	21.84^{B}
Globulin		0.002**	30.2^{A}	31.8^{B}	31^{AB}
Glucose	0.000***	0.002**	4.73^{AB}	4.91^{A}	4.59^{B}
GOT (AST)		0.204	0.38^{A}	0.34^{A}	0.32^{A}
GPT (ALT)		0.12	0.38^{A}	0.28^{A}	0.28^{A}
Homocystein	0.004**	0.969	67.02^{A}	65.24^{A}	65.09^{A}
Iron		0.039*^	13.49^{A}	10.88^{B}	11.95^{AB}
Iron saturation		0.007**	0.2634^{A}	0.1220^{B}	0.1970^{B}
Lipase		0.478	0.50^{A}	0.71^{A}	0.73^{A}
Phosphorus		0.672	1.16^{A}	1.17^{A}	1.18^{A}
Protein total		0.635	70.30^{A}	69.70^{A}	70.20^{A}
Transferrin		0.048*	35.76^{A}	39.04^{A}	35.94^{A}
Triglycerides	0.000***	0.017*	1.25^{AB}	1.34^{A}	1.14^{B}
Urea	0.000***	0.394	8.14^{A}	7.85^{A}	7.85^{A}
Uric acid	0.000***	0.061	242.10^{AB}	253.41^{A}	237.35^{B}
Vitamin B12		0.998	271.76^{A}	270.68^{A}	271.02^{A}
VLDL	0.000***	0.036*	0.56^{A}	0.58^{A}	0.5^{A}

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

^ Was not significant for the mean

□Was not significant for the without outliers

□Was not significant for the mean and without outliers

studying ethnicity as a contributing factor for better health diagnosis and medical outcome [1, 18]. Despite the fact that researchers have recognized ethnic differences in RIs for some biochemical laboratory tests, not many studies have been conducted to study this issue worldwide. The aim of our study was to analyze ethnicity as a contributing factor in common laboratory tests, comparing major ethnic subpopulations in Israel. Israel is an immigration country represented by several ethnic and intra-ethnic groups. Of 27 biochemical analytical values studied, almost half [9] were found to have significant ethnicity-based effects; in most of those biochemical values, Ashkenazi Jews showed the highest mean values compared to Bedouins, with Sephardic Jews exhibiting in-between median values. In two of the biochemical tests, the opposite was demonstrated: Bedouin ethnicity showed the highest mean values and Ashkenazi and Sephardi Jews showed lower median values. For example, significantly low mean cholesterol values (e.g., cholesterol, HDL, and LDL calc.) were evident in Bedouins compared to the mean of Ashkenazi Jews, with Sephardic Jews presenting an in-between value (HDL) or values similar to those of Bedouins (cholesterol and LDL calc.). In contrast, the mean values for triglycerides and creatinine were significantly higher in Bedouins compared to the mean values of Ashkenazi for creatinine and to Sephardic Jews for triglycerides. These results could indicate that different treatment strategies should be considered for different ethnicities as high LDL and low HDL values are established independent cardiovascular disease (CVD) risk factors [27]. While all Israeli ethnicities showed borderline low HDL values, Bedouin women exhibited off the normal range low HDL values, indicating either that they have

Table 4 Summary of parameter estimates of the quantile regression analysis (based on median values) of lower limit ($Q = 0.025$)

	Age	Origin	Ashkenazi	Bedouin	Sephardi
Albumin	0.000***^	0.44	27.1^{A} (0.13)	28.9^{A} (0.13)	28.2^{A} (0.08)
Alk. phosphatase	0.009**^	0.024*^	0.66^{A} (1.53)	0.77^{BC} (1.56)	0.69^{AC} (1.00)
Amylase		0.976	0.50^{A} (3.89)	0.48^{A} (5.08)	28.50^{A} (2.68)
Bilirubin total		0.005**^	5.13^{A} (0.02)	3.42^{BC} (0.02)	4.28^{AC} (0.01)
Calcium		0.141	2.11^{A} (0.23)	2.02^{A} (0.22)	1.98^{A} (0.15)
Cholesterol	**0.017***	0.07	3.52^{A} (5.04)	3.05^{A} (5.23)	3.09^{A} (3.31)
Cholesterol HDL		0.396□	0.53^{A} (1.58)	0.54^{A} (1.61)	0.48^{A} (1.02)
Cholesterol LDL		0.615	1.53^{A} (6.37)	1.66^{A} (7.73)	1.41^{A} (4.00)
Cholesterol LDL calc.		0.373□	65.00^{A} (3.95)	55.00^{A} (4.03)	56.50^{A} (2.58)
Creatinine	0.007**^	0.061□	42.43^{A} (0.02)	36.24^{A} (0.02)	38.01^{A} (0.01)
Folic acid	**0.009****	**0.009****	9.31^{AB} (0.49)	10.24^{A} (0.47)	6.62^{B} (0.32)
Globulin		0.09	23.5^{A} (0.07)	26^{A} (0.07)	25.5^{A} (0.05)
Glucose		0.44	3.91^{A} (2.25)	3.89^{A} (2.23)	3.72^{A} (1.46)
GOT (AST)		0.316	0.18^{A} (0.65)	0.21^{A} (0.64)	0.21^{A} (0.42)
GPT (ALT)		0.466	0.13^{A} (0.80)	0.12^{A} (0.79)	0.11^{A} (0.52)
Homocystein		0.067	34.03^{A} (0.32)	26.63^{A} (0.32)	31.81^{A} (0.19)
Iron		0.873	3.85^{A} (3.61)	3.31^{A} (4.13)	3.76^{A} (2.26)
Phosphorus		0.428	0.90^{A} (0.16)	0.84^{A} (0.16)	0.84^{A} (0.10)
Protein total		0.311	58^{A} (0.27)	52^{A} (0.26)	55.5^{A} (0.17)
Transferrin		0.757	27.37^{A} (11.34)	25.28^{A} (15.13)	26.32^{A} (7.65)
Triglycerides		0.069	0.62^{A} (4.85)	0.43^{A} (4.95)	0.54^{A} (3.19)
Urea	**0.000*****	0.673	4.68^{A} (0.83)	4.61^{A} (0.85)	4.29^{A} (0.54)
Uric acid	**0.000*****	0.199	147.52^{A} (0.16)	155.85^{A} (0.16)	134.44^{A} (0.10)
Vitamin B12		0.019*^	138.71^{AB} (12.76)	150.51^{A} (12.65)	124.69^{B} (8.10)
VLDL		0.488	0.26^{A} (1.00)	0.21^{A} (1.05)	0.23^{A} (0.65)

Bold—significant results both in median-based analysis and mean-based analysis

^ Significant results in median-based analysis only

□Significant results in mean-based analysis only

lower normal ranges for HDL or that they should be considered as having higher risk for CVD, which calls for intervention programs and special medical attention. All ethnicities had normal LDL mean values, with Bedouins showing significantly lower total and LDL cholesterol values compared to Ashkenazi Jews, resulting in almost similar LDL/HDL ratio values (3.08 vs. 3.09, respectively); while Sephardic Jews exhibited lower ratio value (2.97). The cholesterol (cholesterol)/HDL ratio values of all ethnicities were > 4.5 (5.3, 5.28, and 5.24 in Ashkenazi, Bedouin, and Sephardi, respectively). Individuals with a high cholesterol/HDL or LDL/HDL cholesterol ratio have greater CVD risk owing to the imbalance between the cholesterol carried by atherogenic and protective lipoproteins. Again, these ratio values found are within the primary prevention risk level of > 3, indicating either that Bedouins and Ashkenazi Jews exhibit specifically higher normal ratios or that these ethnic groups need advanced medical attention to prevent CVD compared to Sephardic Jews. In relation to CVD risk, LDL/HDL cholesterol may have more predictive power if triglyceridemia is taken into account [28]. Bedouin ethnicity showed significantly higher triglycerides mean values compared to Sephardic and Ashkenazi (in-between) Jews. The VLDL and triglycerides values of all ethnicities were in normal RI range; however, there was a shift towards higher values in Bedouin ethnicity. Ethnicity-related lipid profile studies are scarce; however, a study by Sliwa et al. [29] showed major blood lipid differences between ethnicity groups in patients diagnosed with heart disease in Soweto, South Africa, with clear differences in cholesterol and LDL calc. and triglycerides across ethnicities. Although similar studies were not done in Bedouins, a high prevalence of CVD was recorded in Arab nations with similar ethnicity to Bedouins [30]. Our findings of ethnicity-related differences in lipid profile could contribute a possible explanation for the relatively high risk described in the above study.

Iron saturation (and to some extent also iron) mean levels were significantly lower in Bedouins compared to Ashkenazi Jews, with Sephardic Jews exhibiting similar values (iron saturation). In fact, iron and iron saturation mean values of Bedouins were below the minimal normal range, exhibiting bona-fide iron deficiency. Biochemical indicators of iron

Table 5 Summary of parameter estimates based on quantile regression analysis (based on median values) of upper limit ($Q = 0.975$)

	Age	Origin	Ashkenazi	Bedouin	Sephardi
Albumin	0.024*^	0.595	46.4^{A} (0.5)	45.6^{A} (0.5)	46.3^{A} (0.3)
Alk. phosphatase		0.869	2.37^{A} (45.65)	2.94^{A} (45.30)	2.92^{A} (29.91)
Amylase		0.832	1.80^{A} (65.02)	2.78^{A} (85.28)	2.82^{A} (45.00)
Bilirubin total		0.097	23.95^{A} (0.16)	15.39^{A} (0.15)	17.10^{A} (0.10)
Calcium		0.776	2.52^{A} (0.19)	2.48^{A} (0.19)	2.48^{A} (0.12)
Cholesterol		0.467	6.73^{A} (11.29)	6.16^{A} (11.52)	6.45^{A} (7.40)
Cholesterol HDL		0.020*^	1.94^{A} (4.06)	1.53^{BC} (4.13)	1.84^{AC} (2.61)
Cholesterol LDL		0.439	4.95^{A} (17.08)	4.22^{A} (20.60)	4.38^{A} (10.64)
Cholesterol LDL calc.		**0.000*****	178.00^{A} (8.08)	139.50^{BC} (8.23)	172.00^{AC} (5.27)
Creatinine	**0.009****	**0.000*****	74.26^{A} (0.03)	65.42^{BC} (0.04)	74.26^{AC} (0.02)
Folic acid		0.965	19.30^{A} (2.27)	18.40^{A} (2.10)	19.24^{A} (1.44)
Globulin		0.118□	36^{A} (0.16)	40.5^{A} (0.16)	38^{A} (0.10)
Glucose		**0.016***	7.05^{AB} (10.18)	8.60^{A} (10.02)	6.16^{B} (6.62)
GOT (AST)		0.007**^	1.29^{A} (17.03)	0.89^{AB} (16.92)	0.53^{B} (11.16)
GPT (ALT)		0.044*^	1.69^{A} (26.37)	0.78^{AB} (26.26)	0.61^{B} (17.28)
Homocystein		0.665	188.92^{A} (17.54)	104.96^{A} (17.70)	156.08^{A} (10.33)
Iron		0.015*^	23.63^{AB} (26.12)	20.23^{A} (30.02)	25.60^{B} (16.41)
Phosphorus		0.689	1.41^{A} (0.17)	1.49^{A} (0.17)	1.42^{A} (0.11)
Protein total		0.334	79^{A} (0.12)	80.5^{A} (0.11)	79^{A} (0.08)
Transferrin		0.941	52.52^{A} (65.12)	58.06^{A} (87.07)	52.46^{A} (43.71)
Triglycerides		0.539	2.79^{A} (22.52)	2.58^{A} (22.97)	2.95^{A} (14.77)
Urea	0.031*^	0.666	12.32^{A} (2.71)	13.25^{A} (2.75)	12.37^{A} (1.76)
Uric acid		0.916	368.81^{A} (0.35)	377.73^{A} (0.35)	380.70^{A} (0.23)
Vitamin B12		0.942	504.66^{A} (64.90)	492.85^{A} (64.06)	517.94^{A} (41.24)
VLDL		0.422	1.32^{A} (4.29)	1.14^{A} (4.48)	1.11^{A} (2.78)

Bold—significant results both in median-based analysis and mean-based analysis

^ Significant results in median-based analysis only

□Significant results in mean-based analysis only

metabolism are partly known to be diverse among different ethnicities; however, they have not been sufficiently well studied throughout the world. In a large population of African-American and white subjects undergoing health screening, Beutler and West [31] found that whites had higher hematocrit levels, higher hemoglobin levels, higher MCVs, higher TSs, and lower serum ferritin levels than did African-Americans [31]. Blood iron levels are highly influenced by nutrition; thus, one cannot rule out the role of nutrition as a possible cause of the significant low iron and iron saturation levels in the Bedouins. The fact that transferrin levels in Bedouins were high compared to the other ethnicities might be indicative of possible anemia due to lack of sufficient dietary iron. In fact, high prevalence of iron deficiency was found in a previous study in a similar population of Israeli Bedouins [32].

The difference in the mean (and median) biochemical values may partly be attributed to variations in nutritional status. Lifestyle and nutrition can play a major role in morbidity and mortality as well as in health within populations [33–37]. Using FFQ (Food frequency questionnaire), Abu-Saad et al. [38] delineated nutritional differences between Arab and Jewish population in Israel. It should be noted that Bedouins represent only a portion of the Arab population in Israel and thus might not share all the differences found in Abu-Saad's study. According to Abu-Saad et al., participants in the top Ethnic intake tertile (97% Arab) had modified Mediterranean-style Arabic dietary habits, whereas those in the bottom Ethnic tertile (98% Jewish) had central/northern European-style dietary habits. For instance, in our study, women of Bedouin Arab origin exhibited significantly lower values for albumin, cholesterol, HDL, LDL calc., folic acid, and iron saturation compared to women of Ashkenazi Jews origin. These differences might reflect a consequence of modified Mediterranean/Arab diet, which is rich in olive oil and relatively low in saturated fat. Targeting a similar population, Abu-Saad et al. [39] reported lower iron intake of Bedouin pregnant women, suggestively due to their traditional nutrition with wheat-based foods with low iron bioavailability.

In order to further define ethnicity-related biochemical differences, we took an additional step and analyzed upper and lower parameter estimates based on quantile regression analysis using

the median and mean values of the different ethnicities. We found that in four biochemical values, significant ethnic differences were found in either lower or upper percentile. Compared to the Ashkenazi group, the only biochemical parameter that had a significant origin result in both the median- and the mean-based analysis with a significant shift to lower values was folic acid: Bedouins was significantly higher than Sephardic Jews but both these origins did not differ significantly from Ashkenazi Jews. If our estimated normal ranges are close to true RI for this ethnic group, many Sephardic Jews with lower folic acid would be considered as having high risk of anemia, resulting in unnecessary medical diagnosis and treatment. The biochemical parameter that had a significant origin result in both the median- and the mean-based analysis with a significant shift to higher values were cholesterol LDL calc. and creatinine, where the Ashkenazi Jews were significantly higher than both Bedouin and Sephardic Jews who did not differ significantly from each other, and glucose, where Bedouins were significantly higher than Sephardic Jews but both these origins did not differ significantly from Ashkenazi Jews.

As in all epidemiological studies, the study design has advantages and disadvantages. We have attempted to minimize the limitations of the study through targeting specifically apparently healthy women at fertility age only. Moreover, in terms of the statistical data analysis, we employed multi-statistical approaches, including using median, mean, and mean without outliers data to ensure accuracy of results. Using two different analyses enhances the validity of our approach to studying ethnicity-related biochemical values.

As in any study, our analysis has also several limitations: This is not a random sample of healthy women but a cohort of young women attending fertility clinic. Hence, our results should be studied further in additional women population. In addition, each patient had several measured values for each biochemical parameter. To overcome this, we used several strategies: we ensured the quality of the data through access of all medical and electronic data by a professional team; we repeated all analyses twice using the median value for each individual, which is much less affected by outliers as well as the mean value for reassurance of the significant results; in order to minimize outlier values, all analyses were repeated in cases where outliers were identified, excluding them from the analyses; and only women were chosen for the study to exclude sex differences which are known to affect biochemical values. Notwithstanding all our precautions, systematic bias needs to be carefully considered before attributing broad patterns in biochemical profiles according to ethnicity.

In conclusion, our results indicate RI differences for different ethnic groups in Israel. Ethnic-specific RIs will advance precision medicine and could reduce misdiagnosis, which could impact disease development and treatment. Nevertheless, further research is required to validate these results. Physicians and other healthcare providers use the laboratory test results to track clinical outcomes and make clinical decisions, to screen asymptomatic people and to identify those at risk and for early detection of diseases. Therefore, accurate RIs for laboratory tests are important for patients and their caregivers to monitor their health and disease progress. Further studies will be necessary to evaluate the impact of using ethnic-specific RIs to improve health outcomes.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

Human and animal rights and informed consent This article does not contain any studies with animals performed by any of the authors.

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