Ethnicity influences total serum vitamin B_{12} concentration: a study of Black, Asian and White patients in a primary care setting

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ABSTRACT

Aims A growing body of evidence suggests that ethnicity and race influence vitamin B_{12} metabolism and status yet clinical awareness of this is poor, causing doubts regarding diagnosis and treatment. Moreover, deficiency and insufficiency cut-offs are universally applied for this test in most diagnostic settings. The objective of this study was to assess serum vitamin B_{12} concentrations in Black, Asian and White primary care patients in London, UK, particularly in patients of Black or Black British ethnic origin and establish if there is a need for specific reference ranges.

Methods Serum B_{12} results from 49 414 patients were processed between January 2018 and November 2019 using the Architect assay (Abbott Diagnostics) at St. Thomas' Hospital, London, UK. Age, sex and ethnicity data were collected from the laboratory Health Informatics Team.

Results Black patients (n=13 806) were found to have significantly higher serum vitamin B_{12} concentration across all age groups and both sexes, especially Nigerian patients (median B_{12} 505 pmol/L,IQR: 362–727, n=891), compared with Asian and White ethnic groups (p<0.001). Binary logistic regression analysis revealed that the Black or Black British ethnic group had the strongest association with elevated serum B_{12} (>652 pmol/L) (adjusted OR 3.38, 95% CI 3.17 to 3.61, p<0.0001).

Conclusions It is likely that a combination of genetic and acquired/environmental factors are responsible for the ethnic differences in serum B_{12}. This suggests that there is a need for ethnic-specific reference ranges with indications for the incorporation of age and sex too.

INTRODUCTION

Serum vitamin B_{12} (cobalamin, B_{12}) assays measure the total vitamin B_{12} concentration in circulation, namely vitamin B_{12} bound to two binding proteins: haptocorrin (HC) and transcobalamin (TC), circulating as holoHC (holoHC,~80%) and holoTC (holoTC,~20%) respectively.[1] HoloTC is taken up via receptors to meet metabolic demand. Serum B_{12} is the most commonly used laboratory test in routine practice to help diagnose or rule out vitamin B_{12} deficiency, which can have severe neurological and haematological consequences. However, among patients who have their serum vitamin B_{12} concentrations measured for this reason, elevated concentrations are unexpectedly prevalent.[2] Therefore, the pathophysiology of elevated vitamin B_{12} has recently gained more attention in clinical practice.[3 4]

Vitamin B_{12} is not considered toxic at high concentrations; however, it is important to determine if the elevation is due to vitamin supplementation, which is often the case, since other reasons for elevated B_{12} may be clinically significant. Several studies have linked renal, hepatic, infectious and autoimmune diseases, as well as some cancers, to high serum B_{12} concentrations.[5–8] The associations of high serum B_{12} with cancer or liver diseases have been explained by a release of HC from proliferating leukocytes, malignant tissues, damaged hepatocytes and an increased synthesis or decreased clearance of HC and TC proteins,[3 4 9] leading to B_{12} accumulation in the blood. A screening strategy for addressing high serum B_{12} values has been suggested.[3]

There is also evidence demonstrating significant differences in serum B_{12} concentrations among patients from different ethnic and racial groups.[10] Studies from Africa have shown that black people have higher serum B_{12} concentrations than their white counterparts, whereas deficiency is more prevalent in Asian communities.[11 12] The differences in serum B_{12} have led to a diagnostic dilemma as many clinicians are unaware of ethnic influence on B_{12} status, compounded by the fact that deficiency and insufficiency cut-offs are universally applied for this test.

The aim of this study was to evaluate serum B_{12} concentrations in a highly ethnically diverse group of south-east London patients in relation to race and ethnicity, as well as age and sex, and determine whether ethnic-specific B_{12} reference ranges should be developed.

MATERIALS & METHODS

Anonymised serum B_{12} results from patients referred for B_{12} testing from south London primary care clinics were collected from Laboratory Informatics systems. Information about the ethnicity, age and sex of patients was also obtained.

Patients were categorised into five ethnic groups: Asian or Asian British, Black or Black British, White, Mixed and Other. In addition, there were 67 subcategories (country of origin) within these five main ethnic groups. In this work, we focus principally on the Asian or Asian British, Black or Black British and White ethnic groups. Patients were between 0 and 105 years old.

Table 1 Prevalence of study population by age, gender and ethnic group

Serum vitamin B_{12} concentrations (pmol/L)		Low (<138) n=2176	Normal (138-652) n=42 752	High (653-996) n=3041	Very high (>997) n=1449
Median age in years (IQR)		54 (36–69)	50 (35–65)	50 (37–62)	57 (44–73)
Sex, n (% within sex)	Female n=34 079	1472 (4.3%)	29 284 (85.9%)	2261 (6.6%)	1062 (3.1%)
	Male n=15 339	704 (4.6%)	13 468 (87.8%)	780 (5.1%)	387 (2.5%)
Ethnic group, n (% within ethnic group)	White n=25 817	1426 (5.5%)	23 064 (89.3%)	743 (2.9%)	584 (2.3%)
	Asian or Asian British n=3739	223 (6.0%)	3229 (86.4%)	158 (4.2%)	129 (3.5%)
	Black or Black British n=13 806	300 (2.2%)	11 129 (80.6%)	1778 (12.9%)	598 (4.3%)
	Mixed n=1432	60 (4.2%)	1238 (86.5%)	98 (6.8%)	36 (2.5%)
	Other n=4625	167 (3.6%)	4092 (88.5%)	264 (5.7%)	102 (2.2%)

Percentages are displayed as proportions of totals by row.

Serum B_{12} was measured between January 2018 and November 2019 using the Architect assay (Abbott Diagnostics) at St. Thomas' Hospital, London, UK. The reference range used was 138–652 pmol/L (187–883 ng/L). Serum B_{12} concentrations were assigned to one of the following categories: low (<138 pmol/L), normal (138–652 pmol/L), high (653–996 pmol/L) and very high (>997 pmol/L[4]).

The data were analysed using IBM SPSS V.26.0. Descriptive statistics were used for the distribution of serum B_{12} by ethnicity, age and sex. The data were positively skewed, therefore, non-parametric tests were used. The Kruskal-Wallis test was used to determine differences between serum B_{12} concentrations across ethnic groups, categories and sexes.

Binary logistic regression analysis assessed the relationship between elevated serum B_{12} concentrations (>652 pmol/L) with ethnicity, sex and age. A significance level of $p<0.05$ was used and values were adjusted for by the Bonferroni correction for multiple tests.

RESULTS

Between January 2018 and November 2019, 49419 serum B_{12} results were processed. The median age of patients was 50 years (IQR: 36–65) and the median serum B_{12} concentration was 300 pmol/L (IQR: 216–427). Sixty-nine per cent of patients were female. In each ethnic group, most patients (>80%) had a serum B_{12} concentration within the laboratory reference range (138–652 pmol/L). The Asian or Asian British ethnic group had the greatest proportion of low serum B_{12} concentrations, while the Black or Black British ethnic group had the greatest proportion of high and very high serum B_{12} concentrations (table 1).

There was a statistically significant difference in serum B_{12} concentrations between males and females ($\chi^2=111.2$, $p<0.001$). A greater proportion of female patients had high and very high B_{12} concentrations compared with males (table 1).

Across all age groups and both sexes, Black or Black British patients had significantly higher serum B_{12} concentrations

Table 2 Median serum vitamin B_{12} concentrations by age group within each ethnic group with IQR

	Asian or Asian British		Black or Black British		White	
Age group (years)	Median vitamin B_{12} (pmol/L) (IQR)	n	Median vitamin B_{12} (pmol/L) (IQR)	n	Median vitamin B_{12} (pmol/L) (IQR)	n
0–17	365 (255–554)	219	444 (309–655)	772	346 (252–505)	709
18–29	274 (208–348)	359	330 (236–466)	1253	248 (187–331)	3005
30–39	269 (208 – 363)	627	365 (258 – 516)	1989	277 (211 – 376)	4215
40–49	263 (199–375)	681	394 (280–571)	2719	279 (211–374)	3911
50–59	266 (201–395)	506	401 (282–583)	3093	273 (204–373)	4304
60–69	251 (190–410)	590	412 (289–583)	1725	263 (196–357)	3692
70–79	265 (184–420)	463	381 (268–564)	1277	260 (193– 66)	3136
80+	306 (215–469)	294	330 (227–469)	978	256 (190–369)	2845
Grand median (pmol/L) (IQR)	272 (201–396)	3739	383 (269–555)	13 806	269 (201–368)	25 817

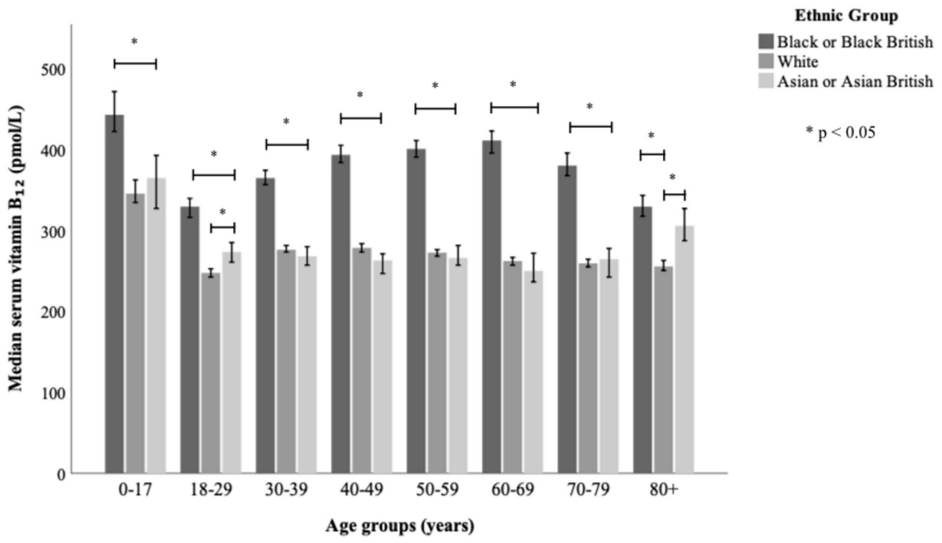

Figure 1 Median serum vitamin B 12 (pmo/L) for age groups within each ethnic group.

(table 2, figures 1 and 2) compared with Asian or Asian British and White ethnic groups (p<0.001).

Children (0–17 years) had significantly higher serum B_{12} concentrations in each ethnic group compared with their adult counterparts (18 years and over) (p<0.001) (figure 1). An overall decline in serum B_{12} concentration was seen as patients got older (Spearman's r: −0.028, p<0.001).

A further look into the vitamin B_{12} levels of children revealed that Black or Black British children had significantly higher B_{12} concentrations than those from Asian or Asian British and White ethnic groups (table 3) (p<0.0001). Black or Black British infants (0–3 years old) had the highest median B_{12} concentration (713 pmol/L (480-942)) (table 3).

The odds of having an elevated serum B_{12} concentration and being a Black or Black British female under 18 years old was higher than the odds of having an elevated serum concentration in any other patient in this study (table 4). Being of Black ethnic origin had the most powerful association with elevated serum B_{12} (adjusted OR 3.38, 95% CI 3.17 to 3.61, p<0.001).

Within the Black or Black British ethnic group, the following subcategories were present: Black British, African, Nigerian, Somali, Caribbean, other Black background and unspecified. The last two categories were excluded from analysis since the backgrounds of these patients were unknown. The highest serum B_{12} concentration was seen in Nigerians (505 pmol/L (362–727), n=891) (figure 3).

DISCUSSION

Primary finding

We found that the Black or Black British ethnic group had significantly higher serum B_{12} concentrations compared with Asian and White people, across all age groups and both sexes.

The exact underlying causes for the differences in serum B_{12} between black patients and their Asian and white counterparts are unknown. However, there are many potential reasons for these findings.

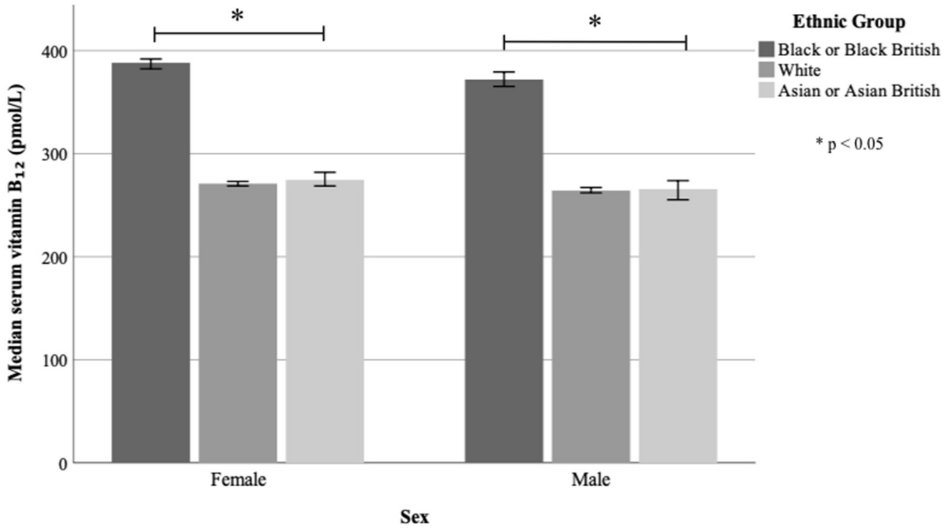

Figure 2 Median serum vitamin B_{12} (pmol/L) for males and females in each ethnic group.

Table 3 Median serum vitamin B_{12} concentrations in children (≤17 years old) within each ethnic group

	Asian or Asian British		Black or Black British		White	
Age groups (years)	Median vitamin B_{12} (pmol/L) (IQR)	n	Median vitamin B_{12} (pmol/L) (IQR)	n	Median vitamin B_{12} (pmol/L) (IQR)	n
0–3	644 (400–764)	22	713 (480–942)	91	473 (349–693)	84
4–8	492 (379–752)	62	632 (518–861)	142	497 (347–610)	177
9–13	314 (258–386)	62	440 (323–631)	225	331 (245–463)	184
14–17	279 (224–394)	73	349 (251–467)	314	270 (210–362)	264
Grand median (pmol/L) (IQR)	365 (255–554)	219	444 (309–655)	772	346 (252–505)	709

Genes

Several genome-wide association studies have suggested that ethnic-specific genetic factors influence vitamin B_{12} status,[13] although evidence of this in non-European populations is limited.[14 15] The Fucosyltransferase 2 (*FUT2*) and Transcobalamin-II (*TCN2*) genes have shown the strongest associations with serum B_{12} concentrations.[16–18]

1,2-*FUT2* is encoded by the highly polymorphic *FUT2 gene* located on chromosome 19. It produces H type 1 and 2 antigens, which act as precursors to each of the ABO blood group antigens. Gastric pathogens such as *Helicobacter pylori* adhere to gastric and duodenal mucosa using these H antigens and can cause infection, interfering with the release of intrinsic factor and leading to B_{12} malabsorption.[19]

Three single-nucleotide polymorphisms (SNPs): rs602662, rs492602 and rs601338 have been most commonly studied regarding their ethnic-specific differences and strong linkage disequilibrium.[18] They are thought to be the strongest causal variants for the association between *FUT2* and serum B_{12} concentration. These SNPs have the following genotypes: GG (secretor variant), AG and AA (non-secretor variant).

The AA (non-secretor) genotype of the rs601338 SNP is the most strongly associated with higher serum B_{12} concentrations in Caucasian populations in the USA, Iceland and Ireland.[16 20 21] It is well known that the most common cause of this non-secretor phenotype is a nonsense mutation, W143X (rs601338 G>A).[18] This encodes a stop codon that inactivates the FUT2 enzyme. Prior hypotheses regarding the mechanism of action causing these higher serum B_{12} levels have focused on the influence of *FUT2* SNPs on the attachment of *H. pylori* to the gastric mucosa. In non-secretors, microbes such as *H. pylori* cannot adhere to the H antigens, therefore, there is a lower chance of vitamin B_{12} malabsorption.[22–25] However, it has recently been found that *FUT2* genotypes can also influence the concentration of holoHC. This is thought to be because of altered fucosylation of HC (whether *FUT2* gene expression directly causes this is still unclear), as HC is a glycosylated protein while TC is not.[21] It is possible that this differential glycosylation of HC can affect the protein's secretion and renal clearance which ultimately contributes to serum vitamin B_{12} levels. Further studies are needed to investigate this relationship further.

Table 4 Binary logistic regression analysis of high (>652 pmol/L) serum vitamin B_{12} concentrations (138–642 pmol/L used as the reference group)

Variables compared	Females vs males	Children vs adults	Black vs non-black	Constant
Crude OR	0.19	0.73	1.22	−2.98
Adjusted OR (95% CI)	1.21 (1.12 to 1.30)	2.07 (1.83 to 2.36)	3.38 (3.17 to 3.61)	0.051 (—)
SE	0.038	0.065	0.034	0.037
Significance (p value)	<0.0001	<0.0001	<0.0001	<0.0001

Nevertheless, approximately 20% of individuals in Caucasian populations have the rs601338 AA non-secretor genotype, whereas a greater number of individuals carry the 'G' allele in Indian populations (23%), which could partly explain the differences in serum B_{12} concentrations between these ethnic groups.[26] In addition to this, it is widely reported that vitamin B_{12} deficiency and suboptimal B_{12} concentrations are prevalent in South Asians, which has been attributed to the high number of vegetarians present in this population.[12] Cultural and religious practices that promote vegetarianism are inherent to certain Indian communities, placing them at greater risk of B_{12} deficiency, especially during pregnancy.[27] As well as significantly lower B_{12} concentrations compared with other ethnicities (White, Black, non-Indian Asian and Latin American), hyperhomocysteinaemia and elevated methylmalonic acid (MMA) concentrations have been found, most notably in Indian men.[28]

Furthermore, the *TCN2* gene, located on chromosome 22, encodes for TC. Variations in the TC protein can affect the binding characteristics of vitamin B_{12} to TC or recognition of the B_{12}-TC complex by the TC receptor (CD320), with possible repercussions on B_{12} availability in the cells.[29]

Higher B_{12}-binding capacities have been seen in Ugandans and Nigerians than in white people,[30–32] which is thought to be linked to higher frequencies of certain *TCN2* alleles in African populations.[33] This could explain why black patients had higher serum B_{12} concentrations than white patients in our study, particularly Nigerians compared with other black backgrounds. Ethnic and racial differences have also been seen in HC concentrations. A study in South Africa found higher levels of plasma HC in black people compared with white people.[34] Similarly, a US study reported higher plasma HC levels in black people compared with other ethnic/racial groups and in women compared with men, which are both consistent with the findings in our study.[35] Furthermore, these differences are not only seen in adults but also in cord blood samples in both Africa and Europe.[36] This, coupled with our finding that Black or Black British infants had the highest median serum B_{12} concentrations in our sample suggests that there may be a strong genetic component underpinning ethnic differences in B_{12} levels.

In our study, only 2.2% of Black or Black British patients were 'B_{12}-deficient' (defined as serum B_{12} <138 pmol/L) compared with 6.0% of Asian or Asian British, 5.5% of White and 4.2% of Mixed patients. Functional markers of status, such as total plasma homocysteine and MMA, were not available. Despite this, studies that have measured these values have found similar results, with B_{12} deficiency (defined as serum B_{12} <258 pmol/L, serum MMA >271 nmol/L and MMA >serum 2-methylcitrate) found to be more common (approximately 2–3 times) in elderly white people compared with African-Americans.[37 38] This may be because there are higher metabolic demands for vitamin B_{12} for which black people must meet, warranting further investigation into whether there are ethnic differences in metabolic requirements, B_{12}-binding capacities and circulating levels of B_{12}-binding proteins to supplement the current literature.[30–34] This can bring us closer to understanding the underlying causes for

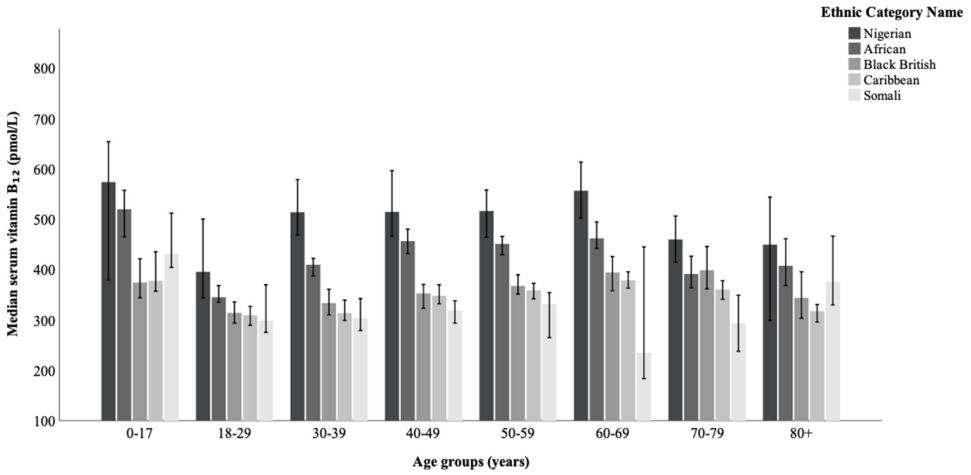

Figure 3 Median serum vitamin B_{12} (pmol/L) for age groups within each black ethnic category.

B_{12} differences and develop more accurate reference ranges to deliver personalised care.

Comorbidities

Alternatively, significant associations between excess serum B_{12} and neoplasms have been reported, and studies have since attempted to identify the diagnostic value of the serum B_{12} assay as an early marker for cancer.[3 39] The carcinomas most frequently seen with elevated serum B_{12} concentrations are hepatocellular carcinoma and secondary liver tumours, followed by breast, colon, stomach and pancreatic cancers.[3] The incidence of primary liver cancer has been reported to be around twice as high in black men than white men,[40] and in a more recent study focused on ethnic groups as opposed to races, Black Caribbean and Black African men had incidence rate ratios of 1.2 and 3.3, respectively.[41] Concurrently, in our study, serum B_{12} concentrations were significantly higher in African patients than Caribbean patients ($p<0.0001$).

Additionally, high serum vitamin B_{12} in autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may be linked to an increase in TC during the acute phase of inflammation.[42] Diseases like RA and SLE are more common in females, which could provide a possible confounding explanation, although one with small effect, for some of the higher concentrations seen in females.[43 44]

Secondary findings

Our results showed that serum B_{12} concentrations decreased with age which coincides with current literature that older patients have lower serum concentrations of B_{12}, as the capacity to absorb B_{12} from a food-based diet decreases with age.[45] This is primarily due to diminished acid secretions in the stomach resulting in decreased whole-body vitamin B_{12} stores, thus placing elderly people at greater risk of B_{12} deficiencies.[46] Likewise, medications such as H_2-receptor (histamine) antagonists and proton pump inhibitors, which block the absorption of protein-bound vitamin B_{12}, are widely prescribed to elderly patients to treat a variety of acid-related conditions.[47]

Another finding was that children in each of the ethnic groups had significantly higher serum B_{12} concentrations compared with their adult counterparts. Some studies have suggested that conditions like autoimmune lymphoproliferative syndrome and zinc deficiency are associated with highly elevated serum B_{12} in children. It is not known how many children in this sample, if any, may have had such comorbidities, or if they were diagnosed on their visit to their primary care provider.[48 49]

Finally, a higher frequency of elevated vitamin B_{12} concentrations was seen in women compared with men yet studies reporting on associations between sex and serum B_{12} concentrations are conflicting. Fernandes-Costa *et al*[50] found that in healthy young adults, unsaturated and total B_{12} binding capacities, HC and serum B_{12} concentrations were significantly higher in females. The mechanisms underlying these differences are not yet known. Another study concluded that elderly males were at a higher risk of folate and B_{12} deficiencies than females.[51] However, other studies have not detected any statistically significant differences in serum B_{12} concentrations between sexes.[33 52]

Limitations

Lifestyle factors, pregnancy, vitamin B_{12} supplementation, medications, multiple measurements for the same patient and comorbidities were not accounted for, which will have had a confounding effect on vitamin B_{12} status.[53–56] The diagnosis of B_{12} deficiency is a complex task as serum B_{12} measurement has limited sensitivity and specificity for diagnosing deficiency.[57 58] A diagnostic gold standard has yet to be found but the key functional markers of B_{12} status, such as total plasma homocysteine, MMA and holotranscobolamin were not measured for these patients. We also cannot confirm to what extent the differences seen were driven by HC abundance.

CONCLUSIONS

Our findings demonstrate that there are significant ethnic differences in serum B_{12} concentrations, with people of a Black

Take home messages

- There were significant ethnic differences in serum B_{12} concentrations observed in this study, with Black/Black British patients having higher concentrations than patients from White and Asian/Asian British ethnic backgrounds.
- A strong hereditary component for elevated serum B_{12} concentrations in black people is likely.
- This work supports the need for ethnic-specific reference ranges with indications for the potential incorporation of age and sex too.

ethnic origin having higher concentrations than White and Asian people. This was seen in all age groups and both sexes. A strong hereditary component for elevated serum B_{12} concentrations in black people is likely. This work supports the need for the future development of ethnic-specific reference ranges with indications for the potential incorporation of age and sex.

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