

Rodrigo Moreno-Reyes  
Yvon A. Carpentier  
Marleen Boelaert  
Khadija El Moumni  
Ghislaine Dufourny  
Christine Bazelmans  
Alain Levêque  
Christine Gervy  
Serge Goldman

## Vitamin D deficiency and hyperparathyroidism in relation to ethnicity: a cross-sectional survey in healthy adults

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R. Moreno-Reyes (✉) · S. Goldman  
Dept. of Nuclear Medicine  
Hôpital Erasme, Université Libre de Bruxelles  
Route de Lennik 808  
1070 Brussels, Belgium  
Tel.: +32-2/555-3300  
Fax: +32-2/555-6800  
E-Mail: rmorenor@ulb.ac.be

Y.A. Carpentier  
Laboratory for Experimental Surgery  
L. Deloyers  
Université Libre de Bruxelles  
Brussels, Belgium

M. Boelaert  
Epidemiology and Disease Control Unit  
Institute of Tropical Medicine  
Antwerpen, Belgium

K. El Moumni · G. Dufourny  
Haute Ecole Lucia de Brouckère  
Campus CERIA  
Brussels, Belgium

C. Bazelmans · A. Levêque  
Ecole de Santé Publique  
Université Libre de Bruxelles  
Brussels, Belgium

C. Gervy  
Dept. of Clinical Chemistry  
Hôpital Erasme, Université Libre de Bruxelles  
Brussels, Belgium

■ **Abstract** *Background* The study of vitamin D status at population level gained relevance since vitamin D deficiency was recently suggested to trigger chronic disease. *Aim of the study* We aimed to describe vitamin D status, its association with bone and mineral metabolism and risk factors for deficiency in adults over 40 years in Belgium. *Methods* We conducted a cross-sectional survey in a stratified random sample of 401 subjects aged between 40 and 60 years living in Brussels, and drawn from 4 different ethnic backgrounds: autochthonous Belgian, Moroccan, Turkish and Congolese. 25-Hydroxyvitamin D (25OHD), parathyroid hormone (PTH), osteocalcin, C-telopeptide and bone mineral density was measured. *Results* Three-hundred and six subjects (77%) showed 25OHD concentrations below 50 nmol/l, 135 (34%) below 25 nmol/l and 18 (5%) below 12.5 nmol/l. The proportion of subjects with vitamin D deficiency was four times greater amongst those of Moroccan or Turkish descent compared with those of

Congolese or Belgian descent. Moroccan subjects showed a significant higher PTH and bone marker concentrations compared to Belgian. Ethnicity, season and sex were independently associated with vitamin D deficiency in multivariate analysis. *Conclusion* The prevalence of vitamin D deficiency is very high amongst the adult population of Brussels but immigrants are at greater risk. Given the established link between population health and adequate vitamin D status, a policy of vitamin D supplementation should be considered in these risk groups.

■ **Key words** vitamin D – ethnicity – bone metabolism – vitamin D deficiency – hyperparathyroidism

## Introduction

Since vitamin D was first described nearly a century ago, its importance in bone metabolism has been well established. Vitamin D deficiency increases the risk of osteoporosis and fractures, while, in its most severe form it causes rickets and osteomalacia. An increasing number of studies suggests that vitamin D deficiency may be a determinant of chronic diseases such as cancer, cardiovascular disease and diabetes as well as infectious disease [2, 15, 21, 22, 29]. The ubiquitous presence of vitamin D receptors in most tissues and accumulating clinical and animal data all support the inference that vitamin D has an essential role in cell proliferation, autoimmune disorders, insulin secretion and tuberculosis [7, 12, 19].

Meanwhile, as the evidence for the implication of vitamin D deficiency in various health disorders mounts, it appears that the prevalence of vitamin D deficiency is greater than previously thought, partly due to the reappraisal of the definition of vitamin D insufficiency [8]. In France, 14% of healthy adults have serum 25OHD concentrations below 30 nmol/l [6], and this proportion may be as high as 29% in countries like Finland [17]. Some population subgroups may be at greater risk of vitamin D deficiency, e.g., the elderly and subjects with darker skin pigmentation or subjects living in regions with low levels of sunlight. Reported prevalence levels within high risk groups rises to 47% amongst elderly people in Europe [32] and 42% amongst Afro-American women in the USA [26].

Because the paucity of population data on vitamin D status in Belgium, the aim of this study was to assess the prevalence of vitamin D deficiency in a population-based survey of adults randomly recruited from four different ethnic groups in Brussels. Vitamin D status, as well as its association with bone and mineral metabolism was determined.

## Methods

### ■ Study subjects

Between 2002 and 2005, the Brussels health authorities conducted a population-survey stratified by ethnic group, of dietary habits and cardiovascular risk factors of all subjects aged between 40 and 60 years. The study on vitamin D status we report here was conducted as a sub-study of this larger survey, as it allowed for a random sample of the population. The protocol for this study was approved by the Ethics Committee of Erasme University Hospital.

Sampling was as follows. In the first stage, a random sample of 1,000 subjects stratified by sex and ethnic group was drawn from the domiciliary registers of seven out of the 19 Brussels municipalities. These municipalities were purposively selected on the basis of both size and proportion of immigrants. The sample was stratified according to the four different ethnic groups living in Brussels: autochthonous Belgians, and first-generation immigrants from Morocco, Turkey and the Democratic Republic of Congo. The classification of ethnicity was observer-assigned and based on the subject's name and own, or parents' country of birth. Second- and third-generation immigrants were excluded from the sample. A home visit was paid to the eligible subjects by a team of trained dietitians. Data on clinical and anthropometric characteristics (weight, height) was collected. Dietary intake of calcium was assessed by interview using a standardized questionnaire, and any use of calcium supplements was noted. The average daily consumption of calcium was calculated.

In a second stage, a random subsample of each ethnic group was invited to Erasme Hospital for further technical investigations related to vitamin D status.

### ■ Biochemical analysis

Morning blood samples were taken from subjects following overnight fasting. Serum PTH was measured by a two-site immunoradiometric assay, whilst serum 25OHD was measured by radioimmunoassay (Diasorin, Stillwater, MN, USA). Routine chemistries were measured by colorimetry (Hitachi Modular-P, Roche Diagnostic, Mannheim, Germany). Serum osteocalcin (intact and the N-MID fragment) and serum C-telopeptide were determined by electrochemiluminescence (Elecys, Roche Diagnostic, Mannheim, Germany). The interassay coefficients of variation were 9–13% for 25-hydroxyvitamin D, less than 7% for osteocalcin and less than 5% for the both parathyroid hormone and C-telopeptide.

### ■ Definition of vitamin D deficiency

Vitamin D deficiency was defined based on 50 nmol/l as the lowest acceptable value for serum 25OHD concentrations [8, 13]. Serum 25OHD concentrations between 25–50 nmol/l indicate mild vitamin D deficiency, moderate vitamin D deficiency correspond to concentrations between 12.5–25 nmol/l and values below 12.5 nmol indicate severe vitamin D deficiency [18].

## ■ Bone mineral density

Bone mineral density was measured by dual-energy X-ray absorptiometry using a Hologic QDR4500 instrument (Hologic Inc., Waltham, MA, USA).

Measurements were taken at the femoral neck and the lumbar spine. The coefficient of variation of repeated measurements at these sites was of 0.71%.

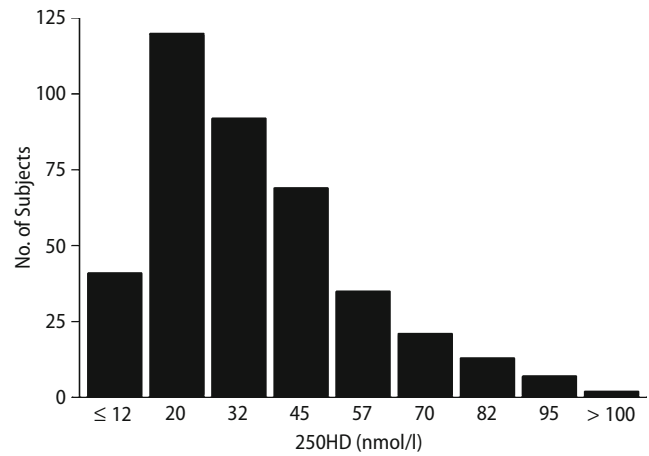
## ■ Statistical analysis

Continuous variables were summarized by their mean ( $\pm$ SD), and means were compared using one-way analysis of variance. To convert continuous variables to binary variables, subgroups were defined using conventional cutoffs employed in epidemiological studies. These included cutoffs for body mass index for normal, overweight and obese subjects and for adequate daily calcium intake  $\geq 1,000$  mg/day. For discrete variables, we compared proportions using Chi-square tests and computed odds ratios with a 95% confidence interval. All *P* values were two-sided. To control for possible confounding factors, adjusted odds ratios were computed by logistic regression. Logistic regression models were fitted to the data using ethnicity as the primary exposure of interest. All variables that were statistically significant in the respective bivariate analysis at the 0.20 level were included in the initial multivariate model. A backwards elimination algorithm was used to generate a "best" final model that included all statistically important variables. Adjusted odds were estimated with 95 percent confidence interval. Statistical analyses were performed using SPSS for WINDOWS, release 10.0.5 (SPSS Inc, Chicago, IL, USA).

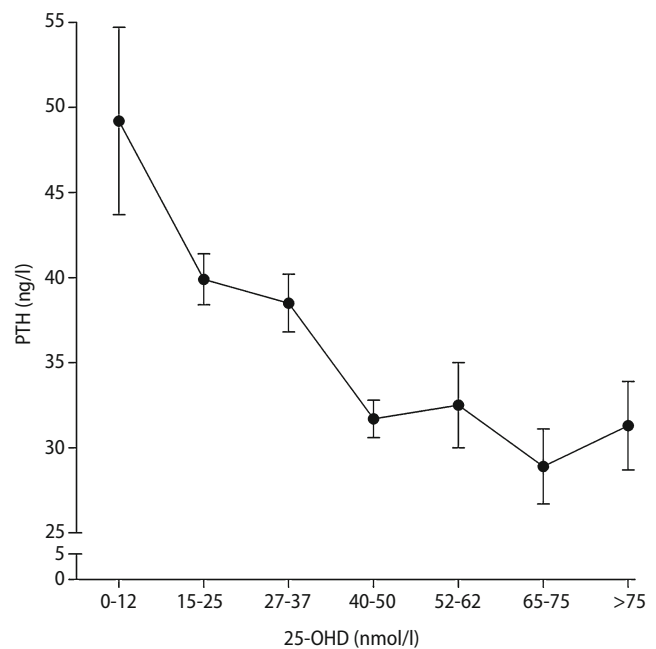
## Results

The prevalence of vitamin D deficiency was estimated at 77% (306/400) (95% CI 72–81%) amongst the population studied (adults living in Brussels). The mean ( $\pm$ SD) and the median (interquartile range) for serum 25OHD concentration for all 400 subjects were  $35.0 \pm 20.0$  and 33.0 nmol/l (20.0–48.0), respectively. Among the 400 study subjects in whom 25OHD was measured, 18 (5%) had serum 25OHD below 12.5 nmol/l, 117 (29%) had values between 12.5 and 24.9 nmol/l, 100 (25%) had values between 25.0 and 37.4 nmol/l and 71 (17%) had values between 37.5 and 49.8 nmol/l (Fig. 1).

Serum PTH concentrations rose for subjects with 25OHD concentrations below 50 nmol/L, indicating a compensatory response to the low serum 25OHD concentrations (Fig. 2).



**Fig. 1** Distribution of serum 25OHD concentrations in 400 subjects from Brussels. The numbers on the horizontal axis represents the midpoints of the interval shown



**Fig. 2** Relation between serum 25OHD and mean ( $\pm$ SE) serum concentrations of PTH in the study population. The patients were categorized according to their serum 25OHD concentrations in increments of 12 nmol/l. Serum 25OHD and PTH were significantly correlated for serum 25OHD <50 nmol/l ( $r = -0.25$ ,  $P < 0.001$ ) but not for concentrations  $\geq 50$  nmol/l ( $r = -0.06$ ,  $P = 0.56$ )

Within the four ethnic groups studied, Belgian subjects were slightly older than the other three groups (Table 1). Bone mineral density was significantly greater in the Congolese subjects than in the other groups. Mean 25OHD concentrations were significantly lower among Moroccan and Turkish immigrants than among Belgian and Congolese subjects. Congolese immigrants exhibited lower serum

**Table 1** Characteristics of the 401 subjects

Characteristics	Belgians		Congolese		Moroccan		Turkish		P value
	Values	No. of subjects	Values	No. of subjects	Values	No. of subjects	Values	No. of subjects	
Age (year)	52 ± 6	101	49 ± 5	99	49 ± 5	100	49 ± 5	101	0.01 <sup>†</sup>
Male sex-no. (%)	51 (50)		49 (49)		50 (50)		51 (50)		1
BMI	27 ± 7	99	28 ± 5	97	28 ± 6	98	29 ± 5	101	0.08
BMD lumbar (g/cm <sup>2</sup> )	1.03 ± 0.14	99	1.13 ± 0.16	97	0.99 ± 0.16	98	1.00 ± 0.13	101	<0.001 <sup>‡‡</sup>
BMD femoral neck (g/cm <sup>2</sup> )	0.79 ± 0.10	99	0.95 ± 0.14	97	0.83 ± 0.12	98	0.82 ± 0.11	101	<0.001 <sup>‡‡</sup>
Serum 25OHD-nmol/l	48.9 ± 22.2	100	38.2 ± 14.2	99	27.2 ± 17.2	100	30.5 ± 20.2	101	<0.001 <sup>§</sup>
Serum 25OHD <12.5 nmol/l, no. (%)	1 (1)		0 (0)		8 (8)		9 (9)		0.002 <sup>¶</sup>
Serum 25OHD <25 nmol/l, no. (%)	13 (13)		14 (14)		54 (54)		54 (53)		<0.001 <sup>¶</sup>
Serum 25OHD <50 nmol/l, no. (%)	60 (60)		76 (77)		90 (90)		80 (79)		<0.001 <sup>¶</sup>
Serum PTH (ng/l)	32 ± 13	100	37 ± 14	99	43 ± 26	100	37 ± 17	101	<0.001 <sup>**</sup>
Plasma calcium (mmol/l)	2.4 ± 0.1	91	2.4 ± 0.1	98	2.4 ± 0.1	98	2.4 ± 0.1	101	0.39
Plasma inorganic phosphate (mmol/l)	1.1 ± 0.1	91	1.2 ± 0.3	99	1.1 ± 0.2	98	1.1 ± 0.1	101	0.006 <sup>††</sup>
Plasma pre-albumin (g/l)	0.34 ± 0.07	91	0.29 ± 0.07	99	0.30 ± 0.05	98	0.29 ± 0.06	101	<0.001 <sup>†</sup>
Serum osteocalcin (nmol/l)	3.1 ± 1.2	101	2.0 ± 1.3	99	3.6 ± 1.2	100	3.6 ± 4	101	<0.001 <sup>¶</sup>
Serum C-telopeptide (pmol/l)	2162 ± 1194	94	2527 ± 1364	91	2906 ± 1566	96	2689 ± 1325	101	0.002 <sup>**</sup>
Calcium intake (mg/day)	954 ± 559	100	527 ± 285	98	763 ± 400	99	793 ± 458	100	<0.001 <sup>‡‡</sup>

P values were derived from one-way analysis of variance or by the chi-square test with Yates' correction. The Scheffé multiple-comparison test was used to compare of means

<sup>†</sup>The value for the Belgian subjects differs significantly from the values for the Congolese, Moroccan and Turkish subjects

<sup>‡</sup>The value for the Congolese subjects differs significantly from the values for the Belgian, Moroccan and Turkish subjects

<sup>§</sup>The value for the Moroccan and Turkish subjects differs significantly from the values for the Belgian and Congolese subjects. The value for the Belgian subjects differs significantly from the value for the Congolese subjects

<sup>¶</sup>The value for the Moroccan and Turkish subjects differs significantly from the values for the Belgian and Congolese subjects

<sup>¶</sup>The value for the Moroccan subjects differs significantly from the values for the Belgian, Congolese and Turkish subjects. The value for the Congolese and Turkish subjects differs significantly from the values for the Belgian subjects

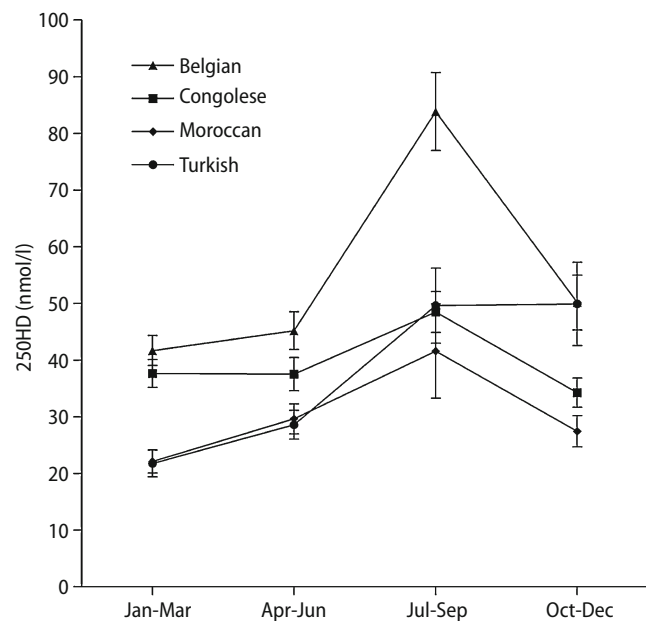
<sup>\*\*</sup>The value for the Moroccan subjects differs significantly from the value for the Belgian subjects

<sup>††</sup>The value for the Congolese subjects differs significantly from the value for the Belgian and Turkish subjects

<sup>‡‡</sup>The value for the Congolese subjects differs significantly from the values for the Belgian, Moroccan and Turkish subjects. The value for the Moroccan subjects differs significantly from the value for the Belgian subjects

25OHD concentrations than native Belgians. The percentage of subjects with 25OHD below 25 nmol/l was high in all groups, but the percentage of Moroccan and Turkish immigrants with 25OHD below 25 nmol/l was four times greater than that amongst Belgian and Congolese subjects. However severe vitamin D deficiency, 25OHD below 12.5 nmol/l, was frequent only in Moroccan and Turkish immigrants. The high frequency of low serum 25OHD concentrations in Moroccans was associated with a greater mean serum PTH, serum osteocalcin and serum C-telopeptide concentrations, indicating secondary hyperparathyroidism and high bone turnover (Table 1). Plasma inorganic phosphate concentrations were greater amongst Congolese than in Belgian and Turkish subjects, and pre-albumin concentrations were greatest amongst the Belgians. The daily calcium intake was lowest in Congolese and highest in Belgians subjects.

Different patterns of seasonal variation in serum 25OHD concentrations could be distinguished between Belgian and all other non-indigenous subjects (Fig. 3). Although all groups had higher serum 25OHD concentrations in the summer compared to winter, the mean serum 25-hydroxyvitamin D values



**Fig. 3** Mean (±SEM) serum 25OHD concentrations by season in Belgian, Congolese, Moroccan and Turkish subjects. In ANOVA, the main effects of season ( $P < 0.001$ ) and ethnicity  $P < 0.001$  and season X ethnicity were significant

**Table 2** Risk of vitamin d deficiency (25OHD <50 nmol/l) in adults inhabitants of brussels

Variable	No. of subjects	No. of cases of vitamin D deficiency (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Age (year)					0.181
40–44	84	59 (70.2)	1	1	
45–49	124	105 (84.7)	2.3 (1.1–4.9)	2.2 (1.0–4.5)	
50–54	103	79 (76.7)	1.4 (0.7–2.8)	1.2 (0.6–2.5)	
55–60	89	63 (70.8)	1.0 (0.5–2.1)	1.2 (0.5–2.5)	
Sex					0.009
Female	200	143 (71.5)	1	1	
Male	200	163 (81.5)	1.8 (1.1–2.9)	2.0 (1.2–3.5)	
Ethnicity					0.003
Belgian	100	60 (60.0)	1	1	
Congolese	99	76 (76.8)	2.2 (1.1–4.3)	1.9 (0.9–3.9)	
Moroccan	100	90 (90.0)	6.0 (2.6–13.9)	4.8 (2.1–11.2)	
Turkish	101	80 (79.2)	2.5 (1.3–4.9)	2.1 (1.1–4.4)	
Months					<0.001
Jan–Mar	148	127 (85.8)	1	1	
Apr–Jun	152	119 (78.3)	0.6 (0.3–1.1)	0.6 (0.4–1.2)	
Jul–Sep	38	16 (42.1)	0.1 (0.1–0.3)	0.1 (0.1–0.3)	
Oct–Dec	62	44 (71.0)	0.4 (0.2–0.9)	0.5 (0.3–1.2)	
BMI					0.121
17–24	119	82 (68.9)	1	1	
25–29	143	108 (75.5)	1.4 (0.8–2.6)	1.1 (0.6–2.0)	
≥30	133	110 (82.7)	2.2 (1.2–4.1)	1.9 (0.9–3.9)	
Calcium intake (mg/day)					0.07
≥1,000	99	66 (66.7)	1	1	
<1,000	301	240 (79.7)	1.9 (1.2–3.4)	1.7 (0.9–3.1)	

P values derived from Wald

OR odds ratio, 95% CI 95% confidence interval, BMI Body Mass Index test

during the summer months remained lower amongst Congolese, Moroccan and Turkish subjects than amongst Belgians.

The multivariate analysis confirmed that ethnic origin is an independent risk factor for vitamin D deficiency in Brussels, with Moroccan subjects exposed to the highest risk, followed by Turkish and Congolese immigrants (Table 2). Belgian subjects experienced the lowest risk. Male subjects were at greater risk of low 25OHD concentrations than females. Seasonality was also an independent risk factor for low 25OHD as prevalence of vitamin D deficiency was greater in winter than in summer. Finally, a borderline increased risk of low 25OHD with BMI was observed.

## Discussion

Prevalence of vitamin D deficiency was very high in this sample of adult residents of Brussels, Belgium, and those from Congolese, Moroccan and Turkish descent were more affected than autochthonous Belgians. Low serum 25OHD concentrations were most frequently observed in Moroccan subjects: 54% had values below 25 nmol/l and 90% had values below 50 nmol/l. Low serum 25OHD concentration is of clinical importance as it triggers compensatory mechanisms such as secondary hyperparathyroidism

and increased bone loss. In our study, because vitamin D depletion was more severe in the immigrants, in particular in the Turkish and Moroccan subjects, the lower serum vitamin D concentrations in these groups, trigger the higher serum PTH concentrations, which stimulate thereby bone resorption as shown by the higher serum concentrations of osteocalcin and C-telopeptide.

In accordance with an international consensus, our study used a lower limit of optimum serum 25OHD concentration as 50 nmol/l [8]. This cut-off corresponded in our study with the value below which PTH concentrations rose, corroborating the clinical relevance of this threshold for our population. Similar increase in serum PTH concentration when serum 25OHD concentrations fall below 50 nmol/l or less have been previously reported in healthy subjects [5, 17, 20], in medical inpatients [31], in subjects with congestive heart failure [35], and in post-menopausal women [14]. However, there is some disagreement concerning the serum 25OHD concentrations triggering the increase of serum PTH as such increase has been reported for serum 25OHD concentrations above 50 nmol/l [6, 8]. Consequently, the debate about the most appropriate cut-off for defining vitamin D deficiency is not closed, as serum concentrations above 75 nmol/l may be associated with better health outcomes in terms of higher bone mineral

density, fewer falls, reductions in fracture risk and greater protection against cancer [3]. If we apply the 75 nmol/l cut-off to our study population, only 7% of subjects would enjoy optimal serum 25OHD concentrations.

Before extrapolating the results to the population at large, the limitations of this study should be acknowledged. Firstly, the study was purposively conducted in municipalities of a capital city with large immigrant communities, which are often characterized as communities of low socio-economic status. Therefore, extrapolation of our data to the general Belgian adult population should only be made with caution, as the autochthonous Belgians in our sample did not necessarily represent a cross-section of the total Belgian population. Nonetheless, the extremely high prevalence of vitamin D deficiency in our study points to a much more serious public health problem than was previously thought to be the case. Secondly, it was not possible to link the ethnic differences we observed to factors as dietary vitamin D intake, clothing style or levels of sun exposure as no such data could be recorded in the general population-survey. Further work is definitely needed to untangle their effects.

Immigrant status is a risk factor of vitamin D deficiency. The problem of high prevalence of vitamin D deficiency among adults in Europe is not new, it was first reported in the 1970s amongst immigrant populations of Asian origin resident in the United Kingdom and more recently in other Europeans countries [9, 24, 25, 28, 33].

Surprisingly, Congolese subjects in our study showed higher values of serum 25OHD concentrations than Moroccan and Turkish immigrants. This suggests that other factors than skin pigmentation such as the socio-economic status or solar UVB exposure may play a role. Because there are very few food items that are rich in vitamin D the differences in vitamin D status are unlikely to be due to higher consumption of food rich in vitamin D. Lumbar and femoral bone mineral densities were significantly higher in Congolese subjects than in the three other groups. This finding is similar to earlier reports showing a higher bone mineral density in Afro-Americans [11]. Their higher BMD has been attributed partially to a greater peak bone mass obtained during the period of adolescent bone growth. Incidentally, calcium retention has also been found greater in Afro-American adolescents compared to white [4]. In addition, genetic differences in body size and a higher muscle mass index may also account for the differences in BMD [27]. Obesity is an important determinant of vitamin D deficiency according to the

literature, and we did observe a borderline increased risk of vitamin D deficiency with BMI [1, 30, 34].

Interestingly plasma prealbumin concentrations were higher in autochthonous Belgian than in the other groups. Plasma prealbumin has been used to assess protein-calorie nutrition [16], however some have challenged this because other factors, like infection, may influence prealbumin concentrations [10]. Most of the studies had used prealbumin in elderly, disease or malnourished subjects. In our study, of healthy adults, prealbumin concentrations were within the normal ranges in all groups. However, the autochthonous Belgian had greater serum prealbumin concentrations suggesting a higher protein-caloric intake than in the immigrant subjects.

Because few natural food items contain vitamin D, our main source of vitamin D stems from the conversion of 7-dehydrocholesterol—the precursor of vitamin D present in the skin—by solar ultraviolet B radiation (UVB) into previtamin D<sub>3</sub>, which is then spontaneously converted into vitamin D<sub>3</sub>. Any factor that decreases UVB photons entering the epidermis will result in a reduction in, or a suppression of, vitamin D<sub>3</sub> production in the skin [12]. In Belgium, as in many regions of Northern Europe, UVB radiation is insufficient to permit skin production of vitamin D in winter [12]. But, the period of the year when skin vitamin D production ceases is likely to be longer for subjects with darker skin pigmentation. Our data suggest that the increase of serum 25OHD during the summer is lower in immigrants than in Belgian subjects. In addition to skin pigmentation, specific styles of clothing may also reduce skin production of vitamin D<sub>3</sub> by preventing UVB radiation entering the skin [23].

Further research to defined optimal vitamin D intake based in health outcomes other than bone health is needed. Prospective studies for treatment and prevention of chronic disease, i.e. cancer and cardiovascular disease are required to truly grasp the impact of vitamin D deficiency and the benefit of increasing vitamin D intake on human health.

In conclusion, our data shows that the prevalence of vitamin D deficiency is extremely high in a population of 40 years and older in Brussels, and that immigrant community runs a higher risk of inadequate vitamin D status than the autochthonous population. Given the well established benefits of an adequate vitamin D status, vitamin D supplementation should be seriously considered in this risk groups and in comparable urban populations throughout Europe.

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