25-Hydroxyvitamin D, IGF-1, and Metabolic Syndrome at 45 Years of Age

A Cross-Sectional Study in the 1958 British Birth Cohort

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OBJECTIVE—Hypovitaminosis D and reduced IGF-1 are associated, individually, with metabolic syndrome. Physiological interactions between vitamin D and IGF-1 are reported; this is the first study to investigate their combined associations with metabolic syndrome prevalence.

RESEARCH DESIGN AND METHODS—Data on 25-hydroxyvitamin D (25(OH)D), IGF-1, and metabolic syndrome abnormalities (abdominal obesity; raised A1C, blood pressure, and triglycerides; and low HDL cholesterol) were collected from 6,810 British white subjects in the 1958 cohort, surveyed during 2002–2004 (age 45 years).

RESULTS—IGF-1 concentrations increased with 25(OH)D up to ~75–85 nmol/l but not thereafter. Both 25(OH)D and IGF-1 were inversely associated with metabolic syndrome. There was an interaction between 25(OH)D and IGF-1 ($P = 0.025$) on metabolic syndrome prevalence: IGF-1 was not significantly associated with metabolic syndrome among those with the lowest levels of 25(OH)D ($P > 0.09$), whereas higher 25(OH)D was associated with metabolic syndrome at all IGF-1 concentrations ($P \leq 0.006$). Metabolic syndrome prevalence was lowest for participants with the highest concentrations of both 25(OH)D and IGF-1 (odds ratio for highest vs. lowest third of both 0.26 [95% CI 0.17–0.40], $P < 0.0001$; adjusted for sex, month, hour, inactivity, alcohol consumption, smoking, and social class). 25(OH)D was associated with the prevalence of high A1C, blood pressure, and triglycerides after adjustment for IGF-1, obesity, and social and lifestyle variations ($P \leq 0.004$ for all comparisons).

CONCLUSIONS—Serum 25(OH)D is inversely associated with metabolic syndrome, whereas the inverse association with IGF-1 was found only among those without hypovitaminosis D. These results suggest that metabolic syndrome prevalence is the lowest when both 25(OH)D and IGF-1 are high. ***Diabetes*** **57:298–305, 2008**

Hypovitaminosis D and reductions in circulating IGF-1 and in certain IGF-1 binding proteins (especially IGFBP-1) have been reported to be associated with metabolic syndrome and its individual components. Both vitamin D status and IGF-1 concentrations are reduced in obesity (1,2); however, for both factors, lower concentrations have been associated with disturbed glucose metabolism (3–8), high blood pressure (9–11), adverse lipid profiles (2,12,13), and cardiovascular disease (8,14,15) independently of body mass. The evidence for associations between vitamin D and IGF-1 axes with metabolic risk includes prospective studies, clinical trials, and dose-related effects, suggesting that associations may prove to be causal. Mechanisms by which vitamin D and IGF-1 axes may lead to human disease are, however, not fully understood, and despite evidence for physiological interaction between these risk factors (16–18), little is known about their joint effects, and we can find no previous studies investigating their combined associations with metabolic syndrome.

Vitamin D is a hormone precursor, which before exerting its metabolic effects undergoes two successive hydroxylations. The first converts vitamin D to 25-hydroxyvitamin D (25(OH)D) (serum concentration of 25(OH)D being an accepted indicator of vitamin D status), and the second converts 25(OH)D to the main active hormonal form, 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$). Hypovitaminosis D appears to act both through reductions in intracellular calcium and through the effects of $1,25\text{-}(OH)_2D$ on the regulation of various target genes (e.g., reduced insulin secretion through reduction in islet β-cell calcium [19], hypertension through lack of suppression of the renin gene [20], certain cancers by dysregulation of relevant target genes [21], and also through dysregulation of immune and anti-inflammatory responses [22]). Mechanisms associating hypovitaminosis D with adverse lipid profiles (12,13) are less well understood.

There is evidence for interrelations between vitamin D and IGF-1 axes; for example, anticancer effects of increased vitamin D availability include promotion of antiproliferative effects on various tissues through increases in IGFBP-1, -3, and -5 production and suppression of cell growth–promoting IGFBP-2 (23). The effects of hormonal vitamin D on the IGF-1 axis follow the targeting of ligand-bound vitamin D receptor complexes to vitamin D response elements in the promoter regions of IGFBP-1, -2, -5, and -6 genes, most of which are known to actively respond to $1,25(OH)_2D$ (23). IGF-1 administration can reduce hyperglycemia in man but can also increase circulating $1,25(OH)_2D$ (17). Thus, IGF-1 could exert effects

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Received for publication 9 August 2007 and accepted in revised form 29 October 2007.

Published ahead of print at http://diabetes.diabetesjournals.org on November 2007. DOI: 10.2337/db07-1122.

1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; IGFBP-1, IGF-1 binding protein; LRT, likelihood ratio test.

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partly through changes in vitamin D activation, whereas $1,25(OH)_2D$ may act in part through changes in IGF-1 axis regulation. These findings provide the basis for interactions between these axes as reported experimentally in bony tissues (24,25) and in observational studies on breast density (18) and adiposity-related factors (16) in humans.

Hypovitaminosis D is a worldwide problem (26,27), as is the increasing prevalence of metabolic syndrome, type 2 diabetes, and cardiovascular disease (28). We have, therefore, examined the associations of both vitamin D status (serum 25(OH)D) and circulating IGF-1 with metabolic syndrome and its individual components in nearly 7,000 participants in the 1958 British birth cohort at age 45 years (29).

RESEARCH DESIGN AND METHODS

Participants are from the 1958 birth cohort, which included all births in England, Scotland, and Wales during 1 week in March 1958 (n = 16,751) (30,31). Most recently, participants were contacted between September 2002 and April 2004, when the majority was aged 45 years [range 44 (31.1%) to 46 (0.4%)]. The target population for the survey consisted of 11,971 individuals currently living in Britain. Seventy-eight percent (n = 9,349) of the participants filled in a questionnaire, of whom 7,591 (81%) also provided blood samples for measurement of serum 25(OH)D and IGF-1 concentrations. The 1958 cohort is almost entirely a white population (98%), and for these analyses, 154 individuals of other ethnic groups were excluded. The main analyses for this study were carried out on 6,810 white subjects with full information on 25(OH)D, on IGF-1, and on all the features of the metabolic syndrome. The 45-year biomedical survey was approved by the South-East Multi-Centre Research Ethics Committee, and written consent for use of information in medical research studies was obtained from the participants.

Weight and standing height, at 45 years of age, were measured without shoes and in light clothing by a trained nurse using standardized protocol and equipment; waist circumference was measured by the nurse midway between the costal margin and iliac crest. Blood pressure was measured in a seated position, after 5 min rest, using an Omron 705CP automated sphygmomanometer with a large cuff for participants with a mid-upper arm circumference ≥32 cm; the measurement was repeated three times, and blood pressure was determined as the average of all successful measurements.

Venous blood samples were obtained without prior fasting and posted to the collaborating laboratory. Serum 25(OH)D concentrations were measured using an automated IDS OCTEIA ELISA with a Dade-Behring BEP2000 analyzer, standardized according to the mean vitamin D external quality assessment scheme (32). Serum IGF-1 concentration was measured using the Nichols Advantage IGF-1 chemiluminescence immunoassay referenced against World Health Organization 1st International Reference Reagent 1988; IGF-1 87/518. Glycosylated hemoglobin (A1C) was assayed using high-performance liquid chromatography standardized to the Diabetes Control and Complications Trial (33). Triglycerides and total and HDL cholesterol were measured by standard autoanalyzer methodology.

Metabolic syndrome was defined using modified criteria of the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (34) as abnormality of three or more of the following: abdominal obesity (waist circumference ≥102 cm in men and ≥88 cm in women), high A1C (>7% or known/self-reported type 2 diabetes) (33,35), high blood pressure (blood pressure ≥140/90 mmHg or use of antihypertensive medication), low HDL cholesterol (<1.0 mmol/l for men, <1.3 mmol/l in women, or use of lipid modifying medications), and hypertriglyceridemia (serum triglycerides ≥2.3 mmol/l [36]).

Potential confounding factors include measurements as follows. Socioeconomic position was assessed using the Registrar General's occupational classification categorized as I and II (managerial and professional), III (nonmanual), III (manual), and IV and V (manual unskilled) from data collected at birth and 42 years (or 33 years if data at 42 years were missing). Individuals who were institutionalized, retired, or long-term unemployed were classified separately. Information on frequency of physical activity was collected at age 42 years (coded as <2–3 times/month, once/week, 2–3 times/week or 4–7 times/week). Time spent watching a television/using a computer daily was reported at age 45 years (coded as <1 h, 1–2 h, and >3 h [29]). Smoking was recorded as none, ex-smoker, 1–19 cigarettes/day, or ≥20 cigarettes/day based on smoking history recorded at ages 23, 33, and 42 years. Frequency and amounts of alcohol consumption were reported at age 42 years (coded as not in the last month, ≤once/month, 2–4 times/month, 2–3 times/week, and >4 times/week); quantity was converted to standard units and coded as none, 1–2 units, 3–4 units, 5–6 units, 7–9 units, and ≥10 units per drinking session. Information on current region of residence was based on Government Office Regions divided into sections as follows: Southern (South-East, South-West, and Greater London), Middle (East Anglia, Midlands, and Wales), England (North, North West, Yorkshire, and Humber), and Scotland.

Statistical analysis. Natural log transformation was used for 25(OH)D and IGF-1 (to achieve normal distributions and for calculating geometric means). Variation in continuous (log transformed) outcomes was evaluated by linear regression and, in dichotomous outcomes, by logistic regression. P values are from log likelihood ratio tests (LRTs); test for trend was preferred where appropriate.

Dichotomous indicators were created for components of metabolic syndrome (i.e., abdominal obesity, high A1C, high blood pressure, low HDL, and high triglycerides), and these were used to create the defined indicator for the syndrome (described above). The main outcome measures in our study are the prevalence of metabolic syndrome and the prevalence of its components, which heretofore we refer to as the metabolic syndrome or as the respective component.

The main analyses were conducted by logistic regression both for the metabolic syndrome and separately for its individual components, adjusting all models for sex, month, and hour (for metabolic syndrome and high triglycerides) of measurement. Initial analyses included graphical examination of data and evaluation of curvature for 25(OH)D and IGF-1 through inclusion of quadratic terms. 25(OH)D and IGF-1 were categorized in thirds (or log transformed) for analysis, and single-term and mutually adjusted models were fitted. Interaction between 25(OH)D and IGF-1 was tested by including an interaction term of continuous log-transformed indicators to the mutually adjusted model (i.e., log 25(OH)D · log IGF1). Because of the observed evidence for a significant interaction between log 25(OH)D and log IGF-1 on their association with metabolic syndrome ($P < 0.05$), we also present data from repeated analyses using a combined indicator for thirds of both 25(OH)D and IGF-1, thereby dividing participants into nine groups. In these analyses, participants in the lowest thirds of both 25(OH)D and IGF-1 are the reference group. Further tests for interaction were done to evaluate possible effect modification by sex and obesity on the association of log 25(OH)D and log IGF-1 (both treated as continuous variables) on the outcome (i.e., on metabolic syndrome and its components), and stratified analyses were performed as warranted. The main modeling for metabolic syndrome was done in four stages: *1*) starting with simple associations with 25(OH)D or IGF-1, *2*) using mutual adjustment for both 25(OH)D and IGF-1, *3*) with additional adjustment for demographic, lifestyle and social factors, and *4*) with further adjustment for adiposity (BMI and waist circumference) for the other components of metabolic syndrome.

A fuller range of potential demographic, lifestyle, and social confounders was investigated; birth weight, family history of diabetes, smoking, frequency and quantity of alcohol consumption, geographical location, frequency of physical activity, time spent watching television or using a computer, and social class at birth and at age 42 years. Adjustments for birth weight, quantity of alcohol, and geographical location were not included in final models because they did not affect the model fit and were not statistically significant (LRT, $P > 0.05$). All analyses were carried out using STATA, version 9.

RESULTS

At age 45 years, 9.6% (n = 315) of men and 8.1% (n = 284) of women had metabolic syndrome (Table 1). Among the individual components of metabolic syndrome, men were more likely to be classified as having disturbed glucose metabolism (2.5 vs. 1.5%, $P = 0.005$), high blood pressure (32.9 vs. 15.3%, $P < 0.001$), and high triglycerides (35.8 vs. 14.1%, $P < 0.001$), whereas the prevalence of low HDL cholesterol and of abdominal obesity was lower in men than in women (4.4 vs. 18.9%, $P < 0.001$, and 29.7 vs. 34.5%, $P < 0.001$, respectively). Abdominal obesity was the most common feature of metabolic syndrome, being present in 94.6% of men and 95.8% of women classified with the syndrome.

Association between 25(OH)D and IGF-1. Lifestyle and social indicators that were associated with the prevalence of metabolic syndrome tended to be associated also with concentrations of 25(OH)D and IGF-1 (Table 1). There was a positive association between 25(OH)D and IGF-1, with a linear increase in IGF-1 until 25(OH)D concentrations reached ~75–85 nmol/l, after which this

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TABLE 1
25(OH)D, IGF-1, and prevalence of metabolic syndrome by sex, BMI, lifestyle, and social characteristics in the 1958 British birth cohort (n = 6,810)

	n (%)	25(OH)D (nmol/l)	IGF-1 (nmol/l)	Metabolic syndrome
Sex				
Men	3,297 (48.4)	53.8	18.0	9.6 (315)
Women	3,513 (51.6)	51.5	17.9	8.1 (284)
P		<0.001	0.51	0.03
BMI (kg/m^2)				
<18.5	37 (0.5)	39.4	15.8	2.7 (1)
18.5–24.9	2,448 (36.0)	54.8	18.2	0.7 (18)
25–29.9	2,808 (41.2)	53.9	18.2	6.3 (178)
30–34.9	1,087 (16.0)	47.9	17.4	22.3 (242)
≥35	430 (6.3)	42.7	16.0	37.2 (160)
P		<0.001	<0.001	<0.001
Physical activity				
<2–3 times per month	1,748 (25.7)	49.6	17.5	11.6 (251)
1 time per week	2,159 (31.7)	52.9	18.2	7.8 (97)
2–3 times per week	1,252 (18.4)	56.0	18.4	7.7 (111)
>3 times per week	1,438 (21.1)	53.6	18.0	7.2 (126)
Unknown	213 (3.1)	51.1	17.6	6.6 (14)
P		<0.001	0.002	<0.001
Smoking				
None	3,196 (46.8)	54.0	18.1	8.0 (255)
Ex-smoker	1,850 (27.2)	54.9	18.0	8.8 (164)
1–19 per day	788 (11.6)	49.7	17.8	8.1 (64)
≥20 per day	755 (11.1)	45.0	17.3	13.3 (100)
Unknown	221 (3.3)	51.2	17.6	7.2 (16)
P		<0.001	<0.001	0.001
Alcohol consumption				
Not in last month	414 (6.1)	45.4	17.5	14.3 (59)
<1 time per month	931 (13.7)	47.0	18.4	12.9 (120)
2–4 times per month	1,465 (21.5)	53.2	18.6	9.0 (132)
2–3 times per week	2,190 (32.2)	55.3	18.1	7.4 (162)
>3 times per week	1,791 (26.2)	54.2	17.3	6.9 (123)
Unknown	19 (0.3)	49.5	17.4	15.8 (3)
P		<0.001	<0.001	<0.001
Family social class (1958)				
I and II (high)	1,318 (19.3)	52.7	18.6	5.8 (77)
III nonmanual	686 (10.1)	54.9	18.2	7.3 (50)
III manual	3,286 (48.3)	53.1	17.8	9.2 (301)
IV and IV	1,325 (19.4)	50.8	17.6	11.6 (154)
Other*	195 (2.9)	48.7	17.3	8.7 (17)
P		0.007	<0.001	<0.001
Adult social class (2000)				
I and II (high)	2,779 (40.8)	53.3	18.4	7.9 (220)
III nonmanual	1,432 (21.0)	52.7	18.0	6.9 (99)
III manual	1,262 (18.5)	53.5	17.6	10.9 (138)
IV and IV	1,065 (15.7)	50.8	17.2	10.3 (110)
Other*	272 (4.0)	48.3	17.9	11.8 (32)
P		0.004	<0.001	<0.001

Data are n (%), geometric means [25(OH)D and IGF-1], and % (n) (metabolic syndrome). *P* values are from linear regression for analyses on log 25(OH)D and log IGF-1 and from a χ^2 test for analyses on metabolic syndrome. IGF-1 and metabolic syndrome are adjusted for sex; 25(OH)D is adjusted for sex and season. *Includes cohort members who are institutionalized, retired, unemployed, and other.

effect reached a plateau (Fig. 1). Adjustment for lifestyle and social factors (listed in Table 1) somewhat attenuated the association between 25(OH)D and IGF-1, and although further adjustment for waist circumference and BMI increased this attenuation effect, a clear independent association of these two variables persisted.

Prevalence of metabolic syndrome by 25(OH)D and IGF-1. Both 25(OH)D and IGF-1 were inversely associated with the prevalence of metabolic syndrome (Table 2). Mutual adjustment had only a small influence; however, there was evidence for interaction between 25(OH)D and IGF-1 on their association with metabolic syndrome (LRT interaction, $P = 0.025$). As shown in Fig. 2, greater IGF-1 was not significantly associated with the metabolic syndrome among participants with the lowest 25(OH)D concentrations (odds ratio [OR] 0.90 [95% CI 0.66–1.20], $P = 0.49$ and 0.77 [0.56–1.05], $P = 0.10$ for the middle and the highest third in IGF-1 compared with the lowest, respectively), whereas greater 25(OH)D was associated with a lower prevalence even among participants in the lowest third of IGF-1 (adjusted OR 0.64 [0.47–0.88], $P = 0.006$ and 0.47 [0.33–0.68], $P < 0.0001$ for the middle and the highest compared with the lowest third of 25(OH)D, respectively). Prevalence of metabolic syndrome was the lowest in

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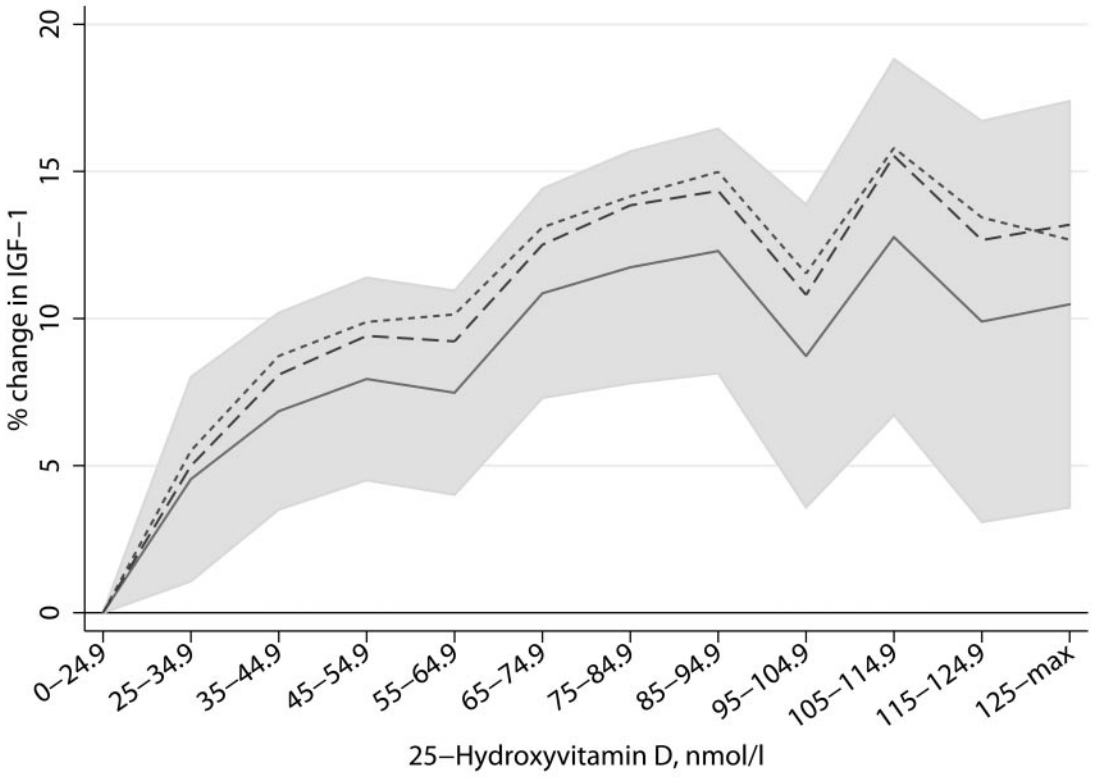

FIG. 1. Variation in IGF-1 by serum 25(OH)D concentration. Model 1 (dashed, short), adjusted for month of measurement and sex. Model 2 (dashed, long), adjusted for month of measurement, sex, lifestyle, and social indicators (physical activity, time spent watching television/using a computer, smoking, alcohol consumption, and birth and adult social class). Model 3 (solid line), adjusted for month of measurement, sex, lifestyle indicators, and adiposity (BMI and waist circumference). Values are coefficients from linear regression (reference <25 nmol/l); 95% CIs presented for model 3 by the shaded area.

participants with the highest concentrations of both 25(OH)D and IGF-1 (OR 0.26 [0.17–0.40], $P < 0.0001$ for highest versus lowest third in both; Fig. 2).

Components of metabolic syndrome by increases in 25(OH)D and IGF-1. All the components used to define metabolic syndrome (abdominal obesity, high A1C, high blood pressure, low HDL cholesterol, and high triglycerides) were significantly associated with 25(OH)D in unadjusted analyses (Table 3). Associations between IGF-1 and components of metabolic syndrome were somewhat weaker than those observed for 25(OH)D, and for abdominal obesity and high serum triglycerides, associations with IGF-1 were observed only in women (LRT interaction, $P < 0.0001$ for both comparisons). There was no evidence of a sex interaction with 25(OH)D in relation to any metabolic syndrome component (LRT interaction, $P \geq 0.2$ for all comparisons). Mutual adjustment for 25(OH)D and IGF-1 had little influence on the associations between 25(OH)D and any of the components, whereas associations for IGF-1 were more strongly affected (the associa-

TABLE 2
Single and joint associations of 25(OH)D and IGF-1 with the metabolic syndrome in the 1958 British birth cohort (n = 6,810)

	Separate models*	Mutually adjusted†	Interaction‡
25(OH)D			
Lowest third (9–45 nmol/l)	Ref.	Ref.	—
Middle third (46–67 nmol/l)	0.56 (0.46–0.69)	0.58 (0.48–0.72)	
Highest third (68–231 nmol/l)	0.31 (0.24–0.39)	0.33 (0.26–0.42)	
Per log unit increase§	0.31 (0.25–0.38)	0.33 (0.27–0.41)	2.01 (0.41–9.95)
P	<0.0001	<0.0001	0.390
IGF-1			
Lowest third (0–16 nmol/l)	Ref.	Ref.	—
Middle third (17–20 nmol/l)	0.76 (0.62–0.93)	0.81 (0.66–0.99)	
Highest third (21–72 nmol/l)	0.59 (0.48–0.73)	0.67 (0.54–0.83)	
Per log unit increase§	0.39 (0.30–0.52)	0.48 (0.36–0.63)	5.44 (0.63–46.8)
P	<0.0001	<0.0001	0.123
log 25(OH)D · log IGF-1	—	—	0.52 (0.30–0.92)
P			0.025

Data are OR (95% CI). *Adjusted for sex, month, and hour of measurement only. †Adjusted for sex, month, hour of measurement, 25(OH)D, and IGF-I. ‡As mutually adjusted with interaction term (log 25(OH)D · log IGF-1). §25(OH)D and IGF-1 in models as continuous, natural log transformed. Estimates can be interpreted as a threefold increase in original scale, for example from 25 to 75 nmol/l.

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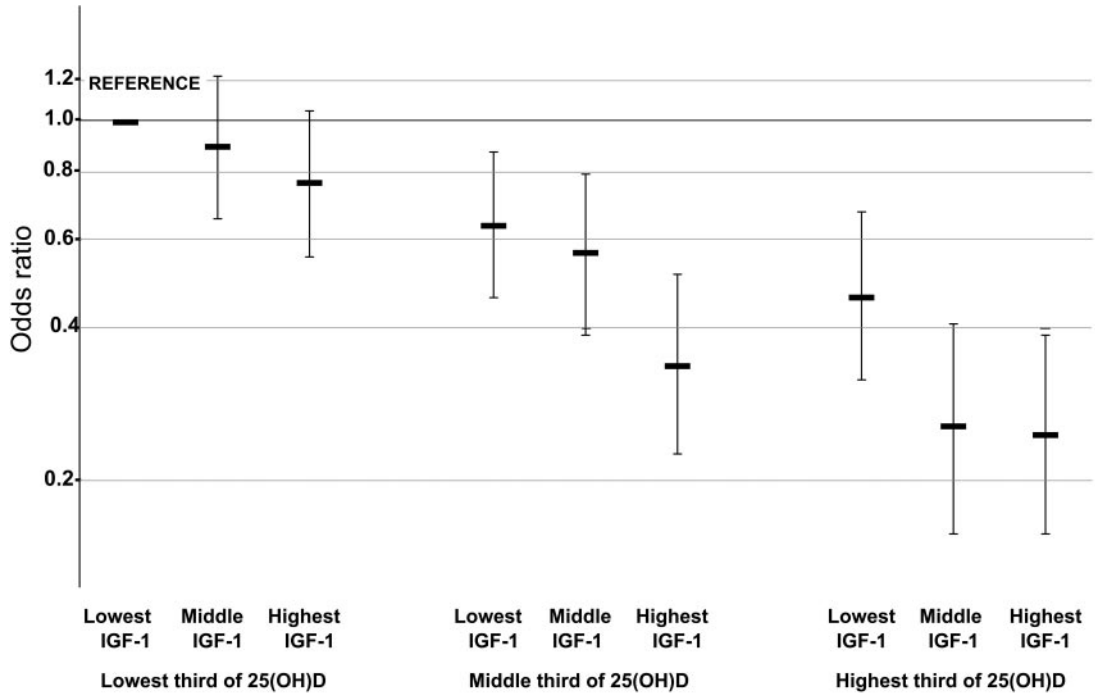

FIG. 2. Interaction between 25(OH)D and IGF-1 on the prevalence of metabolic syndrome; the 1958 British birth cohort (n = 6,293). Values are ORs compared with the lowest thirds of both 25(OH)D and IGF-1 (95% CIs presented by error bars) after adjustment for sex, month, hour, inactivity, alcohol consumption, smoking, and birth and adult social class. Thirds in 25(OH)D: lowest, 10–45 nmol/l; middle, 46–67 nmol/l; and highest, 68–231 nmol/l; thirds in IGF-I: lowest, 0–16 nmol/l; middle, 17–20 nmol/l; and highest, 21–72 nmol/l.

tion with low HDL cholesterol was fully explained). Associations for 25(OH)D with abdominal obesity, A1C, high blood pressure, and high triglycerides, but not with low HDL cholesterol, remained strong after full adjustment for IGF-1, lifestyle and social factors, and obesity (Table 3). Associations for IGF-1 with abdominal obesity and high triglycerides persisted among women in fully adjusted models, whereas borderline associations with A1C and high blood pressure were observed for both sexes. There was no evidence for interaction between 25(OH)D and IGF-1 in relation to any of the individual components of metabolic syndrome (LRT interaction, $P \geq 0.08$ for all). Associations for 25(OH)D with all components of the metabolic syndrome were similar for obese and nonobese participants (LRT interaction, $P > 0.19$ for all comparisons), whereas associations between IGF-1 and high triglycerides were seen in obese participants (lifestyle-adjusted OR 0.84 [95% CI 0.67–1.07] and 0.70 [0.55–0.89], $P = 0.0003$) but not in nonobese participants (1.07 [0.87–1.3] and 1.2 [0.99–1.5], $P = 0.30$; LRT interaction, $P = 0.0006$). There were no interactions by obesity in the association of IGF-1 with any other component (LRT interaction, $P > 0.13$ for all comparisons).

DISCUSSION

These findings from the 1958 British birth cohort (aged 45 years) confirm inverse associations for both 25(OH)D and IGF-1 with the metabolic syndrome (3,8,14). In addition, examination of the interactions between these factors further suggests that the associated reductions in the prevalence of metabolic syndrome may be greatest when levels of both 25(OH)D and IGF-1 are high. 25(OH)D concentration was inversely associated with metabolic syndrome regardless of IGF-1 concentration, whereas no significant variation in metabolic syndrome by IGF-1 concentrations was observed if 25(OH)D concentrations were low. Interestingly, these findings are in accordance with previous observations on mammographic breast density and cancer risk (18), suggesting that the metabolic efficacy of IGF-1 in various tissues may vary according to the individual's vitamin D status.

Metabolic interaction has been reported between the vitamin D and IGF-1 axes experimentally with evidence to show that IGF-1 exerts some effects through changes in vitamin D activation while $1,25(OH)_2D$ in turn modulates the regulation of IGF-1 axis genes (16–18,37). We demonstrate a clear positive association between higher vitamin D status and increased circulating IGF-1 concentration, an association independent of important putative confounders, such as lifestyle factors and adiposity. Circulating IGF-1 was observed to increase steeply up to, but not above, serum 25(OH)D concentrations of 75–85 nmol/l. The suggestion of a plateau for the association between 25(OH)D and IGF-1 at around 75–85 nmol/l is intriguing in light of accumulating evidence suggesting that optimal adult 25(OH)D concentrations are likely to be ≥75 nmol/l (38). Support for this cutoff as a possible optimal concentration has been obtained in relation to various health outcomes (many bone-related), and we have previously shown a steep decrease in average A1C concentrations with higher 25(OH)D concentrations up to 65 nmol/l with only small reductions at higher concentrations (6).

We have previously reported that the association of 25(OH)D with continuous A1C is more marked in obese compared with normal-weight individuals (6), whereas in the current study, the association of 25(OH)D with high A1C (>7% or type 2 diabetes) did not vary by obesity. This may reflect lesser power in interaction analyses on dichotomous outcomes or suggest that much of the previously reported interaction is explained by 25(OH)D influence on

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TABLE 3
OR of having each component of the metabolic syndrome by thirds of serum 25(OH)D and IGF-1 in the 1958 British birth cohort (n = 6,293)

	25(OH)D			IGF-1		
	OR (95% CI)*	Mutually adjusted†	Fully adjusted‡	OR (95% CI)*	Mutually adjusted†	Fully adjusted‡
Abdominal obesity				Men		
Lowest third	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle third	0.63 (0.55–0.72)	0.64 (0.56–0.74)	0.66 (0.58–0.76)	0.87 (0.72–1.1)	0.92 (0.76–1.1)	0.92 (0.75–1.1)
Highest third	0.39 (0.34–0.45)	0.40 (0.35–0.47)	0.44 (0.38–0.51)	0.98 (0.81–1.2)	1.06 (0.87–1.3)	1.07 (0.88–1.3)
Per log unit increase§	0.40 (0.35–0.45)	0.41 (0.36–0.47)	0.44 (0.38–0.50)	0.97 (0.74–1.3)	1.12 (0.85–1.5)	1.13 (0.86–1.5)
P	<0.0001	<0.0001	<0.0001	0.8	0.4	0.4
				Women		
Lowest third	—			Ref.	Ref.	Ref.
Middle third				0.72 (0.60–0.86)	0.74 (0.62–0.88)	0.73 (0.60–0.88)
Highest third				0.55 (0.46–0.66)	0.60 (0.50–0.72)	0.60 (0.50–0.72)
Per log unit increase§				0.39 (0.31–0.50)	0.44 (0.34–0.56)	0.46 (0.36–0.59)
P				<0.0001	<0.0001	<0.0001
High A1C						
Lowest third	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle third	0.43 (0.28–0.66)	0.45 (0.30 0.70)	0.63 (0.40–0.98)	0.67 (0.43 1.0)	0.74 (0.47–1.1)	0.79 (0.50–1.3)
Highest third	0.14 (0.08–0.26)	0.15 (0.08–0.29)	0.30 (0.16–0.57)	0.60 (0.38–0.93)	0.71 (0.45–1.1)	0.77 (0.48–1.2)
Per log unit increase§	0.21 (0.14–0.32)	0.23 (0.15–0.35)	0.39 (0.24–0.63)	0.32 (0.18–0.55)	0.42 (0.24–0.74)	0.52 (0.29–0.97)
P	<0.0001	<0.0001	0.0001	0.0001	0.003	0.04
High blood pressure						
Lowest third	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle third	0.72 (0.62–0.83)	0.73 (0.63–0.85)	0.80 (0.68–0.94)	0.84 (0.73–0.98)	0.87 (0.75–1.00)	0.95 (0.81–1.1)
Highest third	0.57 (0.49–0.67)	0.59 (0.50–0.70)	0.72 (0.61–0.86)	0.72 (0.62–0.83)	0.75 (0.65–0.87)	0.85 (0.73–0.99)
Per log unit increase§	0.59 (0.51–0.68)	0.61 (0.53–0.71)	0.74 (063–0.87)	0.58 (0.48–0.71)	0.63 (0.51–0.77)	0.79 (0.64–0.97)
P	<0.0001	<0.0001	0.0003	<0.0001	<0.0001	0.03
Low HDL						
Lowest third	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle third	0.73 (0.60–0.88)	0.74 (0.61–0.89)	1.00 (0.81–1.2)	0.86 (0.71–1.1)	0.90 (0.74–1.1)	0.96 (0.78–1.19)
Highest third	0.47 (0.38–0.59)	0.48 (0.38–0.60)	0.86 (0.68–1.1)	0.85 (0.70–1.0)	0.92 (0.76–1.1)	1.04 (0.85–1.28)
Per log unit increase§	0.48 (0.40–0.58)	0.49 (0.41–0.59)	0.85 (0.69–1.0)	0.72 (0.56–0.94)	0.82 (0.63–1.06)	1.05 (0.80–1.39)
P	<0.0001	<0.0001	0.13	0.01	0.13	0.70
High triglycerides				Men		
Lowest third	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle third	0.76 (0.66–0.89)	0.77 (0.67–0.90)	0.95 (0.81–1.1)	1.04 (0.86–1.25)	1.07 (0.89–1.29)	1.06 (0.87–1.30)
Highest third	0.48 (0.41–0.57)	0.50 (0.42–0.59)	0.74 (0.61–0.89)	1.03 (0.86–1.24)	1.08 (0.90–1.31)	1.05 (0.86–1.28)
Per log unit increase§	0.51 (0.44–0.60)	0.53 (0.45–0.61)	0.80 (0.64–0.99)	0.97 (0.75–1.3)	1.06 (0.81–1.38)	1.0 (0.75–1.32)
P	<0.0001	<0.0001	0.004	0.81	0.67	0.98
				Women		
Lowest third	—			Ref.	Ref.	Ref.
Middle third				0.67 (0.53–0.86)	0.70 (0.55–0.90)	0.79 (0.60–1.03)
Highest third				0.60 (0.47–0.77)	0.66 (0.51–0.84)	0.81 (0.62–1.06)
Per log unit increase§				0.39 (0.29–0.54)	0.45 (0.32–0.62)	0.63 (0.44–0.89)
P				<0.0001	<0.0001	0.01

Data are OR (95% CI). There was no interaction between 25(OH)D and IGF-I in relation to the individual components of metabolic syndrome ($P > 0.08$ for all comparisons). Associations of IGF-1 with abdominal obesity and high triglycerides, stratified by sex, are shown because of significant effect modification (LRT interaction $P < 0.0001$ for both comparisons). *Adjusted for sex, month of measurement, and hour of measurement for high triglycerides. †Adjusted for sex, month of measurement, and 25(OH)D/IGF-1 as relevant. Analyses on high triglycerides further adjusted for the hour of measurement. ‡Adjusted for sex, month of measurement, and 25(OH)D/IGF-1 as relevant and for physical activity, smoking, alcohol consumption, and birth and adult social class. All but abdominal obesity also adjusted for BMI and waist circumference. Analyses on high triglycerides further adjusted for the hour of measurement. §25(OH)D and IGF-1 in models as continuous, log transformed. Estimates can be interpreted as a threefold increase in original scale, for example from 25 to 75 nmol/l.

severity among participants who already have abnormal glucose metabolism. It is possible that in this relatively young population, metabolic syndrome per se reflects the future risk of cardiovascular or diabetes morbidity better than any single abnormality, and this could explain the lack of interaction for metabolic syndrome components in

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this cohort, despite an interaction for metabolic syndrome. An unexpected finding in our study was the association of IGF-1 with adiposity and high triglycerides in women but not in men. This sex difference may be related to hormonal differences because the women in the present study were premenopausal, but the observation clearly deserves further study.

Methodological considerations. The main strength of the present study lies in the large, population-based sample of participants with information on vitamin D status (serum 25(OH)D), circulating IGF-1, and components of the metabolic syndrome. These data provide adequate power for detailed investigation of associations between these interrelated health indicators. Furthermore, given the extensive information available for the 1958 cohort, we were able to control for many recognized confounding factors, such as social circumstances, lifestyle variations, and body size. Hence, it could be argued that because obesity is a strong determinant of vitamin D status (1,2,6), inclusion of obesity as a confounder may represent overadjustment and that the true association of 25(OH)D with individual components of metabolic syndrome may, therefore, have been underestimated. However, because of the observational cross-sectional design of our study, we are not able to establish specific mechanisms for or to establish causality for these associations.

Our study was restricted to Caucasians, and hence the study does not suffer strongly from problems of population stratification. However, our findings cannot be extrapolated to nonwhite ethnic groups, given the reported heterogeneity by ethnic origin reported for 25(OH)D influences on glucose and lipid metabolism (4). As recently described, some sample attrition has occurred during the survey, and although the present sample remains broadly representative of the surviving cohort, there is some under-representation of specific minority groups (39). An important limitation in our study is that, for practical reasons, fasting samples are not available. Hence, we were not able to adhere to recommended World Health Organization criteria for metabolic syndrome, but we modified it using high A1C concentration to complement information on existing diabetes (33) and using a cutoff for nonfasting triglyceride concentrations based on a screening procedure demonstrated to be effective in identifying diabetes (36,40). The association between IGF-1 and high triglycerides was observed in obese but not in normal-weight participants. As one potential explanation for this association, we have examined whether it was due to the use of nonfasting samples, with obesity interfering with the postprandial increase in triglyceride concentrations. However, we found no statistical evidence suggesting that the association between time since last eating and serum triglycerides was affected by obesity ($P = 0.34$) and no evidence that the interaction between obesity and IGF-1 would have been affected by time since last eating ($P = 0.71$). A further limitation of our study concerns the lack of information on IGFBPs, which limits our ability to evaluate physiological effects of the IGF-1 axis, given that IGFBPs play a major role in the determination of intracellular effects of IGF-1. Nonetheless, the associations found between circulating IGF-1 and metabolic syndrome and, importantly, the interaction found with vitamin D status (25(OH)D) suggest the interdependent involvement of both the IGF-1 and the vitamin D axes in the determination of metabolic syndrome. Further studies are required to establish the mechanisms by which these effects and their interactions are induced, and randomized controlled trials are required to determine the extent to which prevention of hypovitaminosis D might ameliorate the risk of metabolic syndrome.

To conclude, the observed reductions in the prevalence of metabolic syndrome with higher vitamin D status (measured by serum 25(OH)D) were greatest when circulating IGF-1 concentrations were also high, although clear reductions were observed irrespective of IGF-1 concentration. Our results highlight the importance of improving vitamin D status in the general population for the prevention of adverse long-term health risks that hypovitaminosis D may impose both in the U.K. and globally (27).

ACKNOWLEDGMENTS

E.H. has received the Department of Health (U.K.) Public Health Career Scientist Award. Data collection at age 44–46 years and statistical analyses were funded by the UK Medical Research Council (grant G0000934), and the vitamin D sub-study was funded by The BUPA Foundation. Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R&D funding received from the National Health Service Executive.

We thank Dr. Ian Gibb and Steve Turner (Royal Victoria Infirmary, Newcastle-upon-Tyne, U.K.) for carrying out the laboratory assays. Data were provided by Centre for Longitudinal Studies, Institute of Education (original data producers).

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