British Journal of Nutrition (2014), **112**, 992–1003
doi:10.1017/S0007114514001706

Gene polymorphisms and gene scores linked to low serum carotenoid status and their associations with metabolic disturbance and depressive symptoms in African-American adults

May A. Beydoun[1]*, Michael A. Nalls[2], J. Atilio Canas[3], Michele K. Evans[1] and Alan B. Zonderman[1]

[1]*Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIH Biomedical Research Center, IRP 251, Bayview Boulevard, Suite 100, Room 04B118, Baltimore, MD 21224, USA*
[2]*Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA*
[3]*Pediatric Endocrinology, Diabetes and Metabolism, Nemours Children's Clinic, Jacksonville, FL, USA*

(Submitted 30 September 2013 – Final revision received 19 February 2014 – Accepted 31 March 2014 – First published online 24 July 2014)

Abstract

Gene polymorphisms provide a means to obtain unconfounded associations between carotenoids and various health outcomes. In the present study, we tested whether gene polymorphisms and gene scores linked to low serum carotenoid status are related to metabolic disturbance and depressive symptoms in African-American adults residing in Baltimore city, MD, using cross-sectional data from the Healthy Aging in Neighborhoods of Diversity across the Life Span study (age range 30–64 years, *n* 873–994). We examined twenty-four SNP of various gene loci that were previously shown to be associated with low serum carotenoid status (SNPlcar). Gene risk scores were created: five low specific-carotenoid risk scores (LSCRS: α-carotene, β-carotene, lutein+zeaxanthin, β-cryptoxanthin and lycopene) and one low total-carotenoid risk score (LTCRS: total carotenoids). SNPlcar, LSCRS and LTCRS were entered as predictors for a number of health outcomes. These included obesity, National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome and its components, elevated homeostatic model assessment of insulin resistance, C-reactive protein, hyperuricaemia and elevated depressive symptoms (EDS, Center for Epidemiologic Studies-Depression score ≥16). Among the key findings, SNPlcar were not associated with the main outcomes after correction for multiple testing. However, an inverse association was found between the LTCRS and HDL-cholesterol (HDL-C) dyslipidaemia. Specifically, the α-carotene and β-cryptoxanthin LSCRS were associated with a lower odds of HDL-C dyslipidaemia. However, the β-cryptoxanthin LSCRS was linked to a higher odds of EDS, with a linear dose–response relationship. In summary, gene risk scores linked to low serum carotenoids had mixed effects on HDL-C dyslipidaemia and EDS. Further studies using larger African-American population samples are needed.

Key words: Gene polymorphisms: Gene risk scores: Carotenoids: Metabolic disturbance: Depressive symptoms

Oxidative stress, an imbalance between the production of reactive oxygen species and the ability of the cell to scavenge those species with various antioxidants, has been implicated in the pathogenesis of many chronic diseases, including type 2 diabetes mellitus, CVD, rheumatological disorders and carcinogenesis[1]. Potential beneficial effects have recently been ascribed to naturally occurring phytochemicals known as carotenoids which may reduce oxidative stress triggered by injury that characterises the pathogenesis of those chronic diseases[1]. Although the primary dietary sources of carotenoids are fruits and vegetables, they are also found in bread, eggs, beverages (e.g. carrot and tomato juices), fats and oils[2]. Among more than forty carotenoids in the human diet, only the following five carotenoids or groups of carotenoids have been shown to be consistently measurable in human serum: α-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein+zeaxanthin (often combined together)[2].

Some observational studies have shown inverse associations between carotenoids and CVD[3], type 2 diabetes[4–8] and the metabolic syndrome (MetS) in recent national surveys[9–11]. Moreover, in two recent studies, using the National Health and Nutrition Examination Survey (NHANES) and Invecchiare in

Abbreviations: *BCMO1*, β,β-carotene 15,15′-mono-oxygenase; CRP, C-reactive protein; EDS, elevated depressive symptoms; GWAS, genome-wide association studies; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HDL-C, HDL-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LSCRS, low specific-carotenoid risk score; LTCRS, low total-carotenoid risk score; MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHANES, National Health and Nutrition Examination Survey; Q, quartile; *SCARB1*, scavenger receptor class B member 1; SNPlcar, SNP for lower carotenoid status.

* **Corresponding author:** Dr M. A. Beydoun, fax +1 410 558 8236, email baydounm@mail.nih.gov

Chianti (InCHIANTI) data, serum total carotenoid level has been shown to be consistently inversely related to depressive symptoms[12,13]. However, the findings are inconsistent with those reported by other studies[14–17]. It is also worth noting that obesity and its related disorders have been shown to be associated with an increased level of depressive symptoms in a number of studies (e.g. Beydoun *et al.*[18], Kimura *et al.*[19], Akbaraly *et al.*[20]), suggesting co-morbidity between those conditions.

Importantly, it is unclear whether the observed inverse relationships between serum carotenoids and the MetS and/or depression are due to variations in carotenoid concentration or determined by other carotenoid-containing food constituents. To identify an unconfounded role of carotenoids in health and disease, surrogate measures such as genetic polymorphisms have been used in recent studies. In fact, genome-wide association studies (GWAS) and candidate gene studies have uncovered genetic polymorphisms in a number of genes that were significantly associated with serum carotenoid status. Genes carrying the specific SNP that have been commonly tested in the literature against serum carotenoid concentrations were either directly (e.g. β,β-carotene 15,15′-mono-oxygenase, *BCMO1*) or indirectly (e.g. *ApoE*) related to carotenoid metabolism[21–30]. Many of these GWAS and candidate gene studies have been conducted among the individuals of European descent.

Therefore, the overall aim of the present study was to assess whether genetic polymorphisms involved in carotenoid absorption, intracellular trafficking and plasma transport are also related to a higher burden of metabolic disturbance and depressive symptoms. The present study focused on African-American adults who were part of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, providing the first opportunity to examine these relationships within this racial/ethnic group. The findings could elucidate whether metabolic disturbance and/or depressive symptoms are associated with genetic polymorphisms that are in turn related to low serum carotenoid status.

Materials and methods

Database and study population

Initiated in 2004 as an ongoing prospective cohort study, the HANDLS study used area probability sampling to recruit a socio-economically diverse and representative sample of African Americans and whites (30–64 years old) living in Baltimore, MD[31]. The HANDLS protocol was approved by the Institutional Review Board of the National Institute on Aging. The present study used cross-sectional data from the baseline HANDLS study cohort.

A total of 3720 selected subjects participated in the household survey at phase 1 (sample 1). Of these selected subjects, 2436 (65·4 %) had complete baseline phase 2 examinations (sample 2). However, our data used a subset with complete genetic data on a sample of African-American participants of the HANDLS study (*n* 1024, sample 3). Of these subjects, 873 had complete depressive symptom data (sample 4a) and 910–961 had complete data on metabolic outcomes (sample 5a–5i).

Genetic data

Blood samples were collected from the participants for DNA extraction, and genome-wide genotyping was completed for 1024 participants of the HANDLS study using Illumina 1M SNP coverage. For a further description of the methods used, see online supplementary methods.

Selection of SNP of interest for the present analysis was solely based on those detected in previous GWAS and candidate gene studies as highly significant predictors of serum carotenoid status[22,28,32]. These SNP were extracted from high-quality imputed genotypes. Most of these selected SNP are available in our database, with the exception of two β,β-carotene-9′,10′-oxygenase (*BCDO2*) SNP (W80X: bovine SNP; c.196C>T: sheep SNP), which are not human SNP, and one scavenger receptor class B member 1 (*SCARB1*) SNP (SR-BI: intron 5)[22]. Other SNP (*n* 5) that were selected from one study[28] were dropped for various reasons, the most common of which was high linkage disequilibrium with the other selected SNP. None of the remaining SNP was in strong linkage disequilibrium with each other. Consequently, twenty-four distinctive SNP with reliable values were chosen. A detailed description of these selected SNP is presented in online supplementary Table S1.

SNP for lower carotenoid status, low specific-carotenoid risk score and low total-carotenoid risk score. Of the twenty-four distinctive SNP, combinations that would allow the assessment of the effect of an increasing genetic risk of lower carotenoid level on the binary measures of metabolic disturbance and depression were created. First, we examined the independent effects of each SNP allele dosage that was previously shown to be associated with a lower specific carotenoid or a group of carotenoids. To this end, from these twenty-four SNP, twenty-four genetic exposure variables were created and termed SNPlcar (SNP for lower carotenoid status). SNP dosage was coded as is or reverse coded (0,1,2 or 2,1,0) depending on whether the minor allele was associated with lower carotenoid status or vice versa (for details, see online supplementary Table S1).

Moreover, to assess the collective associations of SNP linked to lower levels of specific and total carotenoids with the outcomes of interest, two risk scores were created: (1) low specific-carotenoid risk score (LSCRS), by summing the SNPlcar values together that pertained to that specific carotenoid; (2) low total-carotenoid risk score (LTCRS), by summing all SNPlcar values together, reflecting low levels of all carotenoids (see online supplementary Table S2 and Fig. S1). In the computation of the former score, a SNPlcar was entered into a LSCRS, when previously shown to have the most significant association with a specific carotenoid (smallest *P* value), particularly when multiple carotenoids were affected by the same SNPlcar. We assumed that each SNPlcar was associated with the levels of specific carotenoids based on previous findings in whites, despite potential ancestral differences in African Americans, particularly in terms of linkage disequilibrium patterns[33]. Since a direct way to estimate the effect size of each SNPlcar on the levels of serum carotenoids was not available for African Americans, we did not apply SNP-specific weights from previous studies on whites to

account for SNP-specific differences in the effects on carotenoid status. Thus, we simply summed the risk alleles or the combinations of risk alleles together to obtain the LSCRS and LTCRS, as was done in a previous study[34]. In each LSCRS, SNPlcar included were specific to that particular carotenoid and were not double-counted in another LSCRS.

Anthropometric indices

Body weight and standing height were measured directly. BMI (weight/(height)^2, kg/m^2) was calculated for each participant. Waist circumference (cm) was measured using a tape measure starting from the hip bone and wrapping around the waist at the level of the navel. Obesity was defined as BMI ≥ 30 kg/m^2, while central obesity was defined as a component of the MetS (see the 'Metabolic syndrome' section).

Metabolic outcome variables

Systolic and diastolic blood pressure. The average of the right and left sitting blood pressure values was taken to represent each of the systolic and diastolic blood pressure levels for the present analysis. Blood pressure was measured non-invasively using the brachial artery auscultation method with an aneroid manometer, a stethoscope and an inflatable cuff.

Other metabolic risk factors. Following an overnight fast, blood samples were drawn from an antecubital vein. Total cholesterol, HDL-cholesterol (HDL-C), TAG, uric acid and glucose concentrations were assessed using a spectrophotometer (Olympus 5400). Fasting serum insulin concentration was analysed with a standard immunoassay test (DPC Immulite 2000; Siemens), and C-reactive protein (CRP) concentration was analysed with an immunoturbidimetry method (Behring Nephelometer II; Siemens). Homeostatic model assessment of insulin resistance (HOMA-IR)[35] was computed with a cut-off point of 2·61, reflecting a high insulin resistance level as has been suggested elsewhere[36]. Cut-off values for hyperuricaemia were >420 μmol/l (>7 mg/dl) in men and >360 μmol/l (>6 mg/dl) in women[37], while elevated CRP was defined as $>2{\cdot}11$ mg/l[38].

Metabolic syndrome. Central obesity was defined by waist circumference ≥ 102 cm or 40 inches for men and ≥ 88 cm or 35 inches for women[39]. This is one of the five components in the main definition of the MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (2005)[40]. Using this definition, the MetS was positive when three or more of the following criteria screened were positive: (1) waist circumference >102 cm for men and >88 cm for women; (2) systolic blood pressure/diastolic blood pressure $\geq 130/85$ mmHg; (3) fasting glucose $\geq 5{\cdot}5$ mmol/l (≥ 100 mg/dl); (4) TAG $\geq 1{\cdot}7$ mmol/l (≥ 150 mg/dl); (5) HDL-C $<1{\cdot}04$ mmol/l (<40 mg/dl) for men and $<1{\cdot}3$ mmol/l (<50 mg/dl) for women.

Assessment of depressive symptoms

Extensively trained psychometricians administered, among others, a baseline battery of cognitive and neuropsychological tests[41] that included baseline depressive symptoms using the Center for Epidemiologic Studies-Depression scale, a twenty-item, self-report symptom rating scale that emphasises the affective, depressed mood component[42]. The invariant factor structure of the Center for Epidemiologic Studies-Depression scale was recently shown using confirmatory factor analysis comparing NHANES I and HANDLS data[43]. A cut-off point of 16 was used to assess elevated depressive symptoms (EDS) in all analyses.

Covariates

Covariates considered as potential confounders included sex, age, education (below high school (grades 1–8), high school (grades 9–12), above high school (13+)), poverty income ratio (below *v.* at or above the poverty line), smoking status (current smoker *v.* non-smoker), drug use (current *v.* past or never), and ten principal components to control for any residual effects of the population structure (see online supplementary methods).

Statistical methods

Differences in means and associations of categorical variables across 'genetic data completeness' were tested by t and χ^2 tests, respectively, using Stata 13.0 (StataCorp)[44]. Then, multiple logistic regression models were conducted to test the associations of SNPlcar (entered separately in each model), five LSCRS (entered simultaneously) and one LTCRS with ten binary outcomes (obesity, MetS and five components), elevated HOMA-IR, elevated CRP, hyperuricaemia and EDS. Adjusted OR and 95 % CI were estimated. Type I error was initially set at 0·05, with regression coefficients being assessed using the Wald test. Finally, to test linear dose–response relationships, quartiles of LSCRS and LTCRS were entered into the regression models as ordinal variables, and P values for trend were computed from the Wald test. Additionally, non-linear associations were tested for each quartile compared with the lowest quartile (Q1) as the common referent category. SNPlcar analyses were corrected for multiple testing by reducing type I error to α/k ($k=24$ is the number of SNP tested for each phenotype). Thus, two-sided P values were presented uncorrected, with a significance level being set at $0{\cdot}05/24=0{\cdot}002$.

Results

According to Table 1, the selected participants with complete genetic data were generally older, but had a few missing data on most sociodemographic and lifestyle variables compared with those without genetic data. All LSCRS (in their continuous form) were weakly to moderately correlated (R −0·50 for lutein+zeaxanthin *v.* β-cryptoxanthin to +0·044 for lutein+zeaxanthin *v.* lycopene). Thus, it was possible to covary these gene scores in multiple logistic regression models. For descriptive purposes, mean dietary intakes of carotenoids (μg/4184 kJ per d (μg/1000 kcal per d)) are presented in online supplementary Fig. S2, stratified by sex and poverty income ratio categories. Comparisons were made between

Table 1. Characteristics of the participants of the Healthy Aging in Neighborhood of Diversity across the Life Span (HANDLS) study by genetic data completeness

(Number of participants and percentages; mean values and standard deviations)

	All African-American HANDLS participants (*n* 2198)		African-American HANDLS participants with genetic data (*n* 1024)		African-American HANDLS participants without genetic data (*n* 1174)	
	n	%	*n*	%	*n*	%
Characteristics						
Sociodemographic, lifestyle factors						
Age (years)	2198		1024		1174	
Mean	47·7		48·5		47·0*	
SD	9·3		9·0		9·5	
Female	1200	54·6	569	55·6	631	53·7
Marital status	2198		1024		1174	
Married	610	27·8	427	41·7	183	15·7*
Missing	994	45·2	230	22·5	764	65·0
Education	2198		1024		1174	
< HS	117	5·3	49	4·8	68	5·8*
HS	1421	64·7	638	62·3	783	66·7
> HS	647	29·4	333	32·5	314	26·8
Missing	13	0·6	4	0·4	9	0·8
Poverty income ratio < 125 %	1156	52·6	542	52·9	614	52·3
Current smoking status	2198		1024		1174	
Currently smoking	781	35·5	469	45·8	312	26·6*
Missing	659	30·0	88	8·6	571	48·6
Currently using illicit drugs	2198		1024		1174	
Using any type	806	37·7	513	50·1	293	25·0*
Missing	694	31·6	86	8·4	608	51·8
Depressive symptoms						
CES-D score	1319		873		446	
Mean	11·6		11·7		11·4	
SD	8·0		8·1		7·6	
CES-D score ≥ 16	351	26·6	235	26·9	116	26·0
Metabolic outcomes						
BMI (kg/m^2)	1657		994		663	
Mean	29·9		29·9		30·0	
SD	7·9		8·0		7·8	
Obese (BMI ≥ 30 kg/m^2)	711	42·9	416	41·8	295	44·5
Waist circumference (cm)	1589		961		628	
Mean	98·4		98·5		98·2	
SD	17·5		17·5		17·5	
Centrally obese	892	56·1	543	56·5	349	55·6
SBP (mmHg)	1614		977		637	
Mean	121·5		122·2		120·4	
SD	20·4		20·7		20·1	
DBP (mmHg)	1614		977		637	
Mean	73·0		73·3		72·6	
SD	12·7		12·8		12·5	
Elevated blood pressure	570	35·4	364	37·3	206	32·3*
HDL-C (mmol/l)	1576		989		587	
Mean	1·44		1·43		1·45	
SD	0·48		0·47		0·50	
Dyslipidaemia, HDL-C	479	30·4	304	30·7	175	29·8
TAG (mmol/l)	1577		989		588	
Mean	1·23		1·21		1·28	
SD	0·82		0·76		0·92	
Dyslipidaemia, TAG	288	18·3	178	18·0	110	18·7
Fasting blood glucose (mmol/l)	1578		989		589	
Mean	5·76		5·80		5·67	
SD	2·39		2·38		2·42	
Hyperglycaemia	496	31·4	325	32·9	171	29·0
NCEP ATP III metabolic disturbance	1480		928		552	
Mean	1·71		1·74		1·64	
SD	1·28		1·28		1·29	
NCEP ATP III MetS	396	26·8	260	28·0	136	24·6
HOMA-IR	1561		986		575	
Mean	3·20		3·13		3·32	
SD	4·41		3·90		5·17	
Elevated HOMA-IR	617	39·5	385	39·1	232	40·3

Table 1. *Continued*

	All African-American HANDLS participants (*n* 2198)		African-American HANDLS participants with genetic data (*n* 1024)		African-American HANDLS participants without genetic data (*n* 1174)	
	n	%	*n*	%	*n*	%
CRP† (mg/l)	1518		967		551	
Mean	4·63		4·61		4·66	
SD	6·72		6·73		6·72	
Elevated CRP	741	48·8	466	48·2	275	49·9
Uric acid (μmol/l)	1576		989		587	
Mean	330·1		330·1		330·1	
SD	98·7		98·1		99·9	
Hyperuricaemia	385	24·4	239	24·2	146	24·9

HS, high school; CES-D, Center for Epidemiologic Studies-Depression; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, HDL-cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; MetS, metabolic syndrome; HOMA-IR, homeostatic model assessment-insulin resistance; CRP, C-reactive protein.

* $P<0·05$ for null hypothesis of no difference by genetic data completeness (t or χ^2 test).

† Outliers with values of CRP >50 (*n* 12) were removed from this sample.

the categories, and key findings included a higher intake of β-carotene and lutein+zeaxanthin among women. However, the LTCRS was not correlated with total carotenoid intake (μg/4184 kJ per d (μg/1000 kcal per d)) (R −0·03, P=0·35; see online supplementary Fig. S3).

While examining each of the twenty-four SNPlcar in a separate model as a predictor for each of the outcomes of interest, controlling for key potential confounders (see Table 2 and online supplementary Table S3), a few associations emerged that were against the hypothesised direction. On the one hand, these included a putative inverse relationship between $SNPlcar_{17(BCMO1,\beta\text{-carotene})}$ and obesity; $SNPlcar_{2(APOB,\beta\text{-carotene})}$ and several phenotypes, indicative of inflammation (CRP), dyslipidaemia (low HDL-C) and, importantly, NCEP ATP III MetS; $SNPlcar_{10(BCMO1,\beta\text{-cryptoxanthin})}$ and hypertension; $SNPlcar_{19(CD36,\text{lutein+zeaxanthin})}$ and TAG dyslipidaemia; and $SNPlcar_{23(LPL,\alpha\text{-carotene})}$ and elevated HOMA-IR. On the other hand, a number of SNPlcar showed positive associations that were in line with the hypothesis, mainly within the BCMO1 locus. These included $SNPlcar_{14(BCMO1,\beta\text{-cryptoxanthin})}$ and EDS; $SNPlcar_{12(BCMO1,\alpha\text{-carotene})}$ and central obesity; and $SNPlcar_{14(BCMO1,\beta\text{-carotene})/SNPlcar16(BCMO1,\beta\text{-carotene})}$ and hypertension. However, none of the key findings survived Bonferroni correction.

When combining SNPlcar into gene risk scores reflecting lower levels of specific carotenoids (i.e. LSCRS) and examining their associations with multiple outcomes (Table 3), several findings emerged. First, the α-carotene LSCRS was associated with a lower odds of HDL-C dyslipidaemia (Q_4 (highest quartile) *v.* Q_1 (lowest quartile): OR 0·65, 95 % CI 0·44, 0·97; P=0·037, P for trend=0·045), with a similar pattern being observed for the β-cryptoxanthin LSCRS (Q_4 *v.* Q_1: OR 0·61, 95 % CI 0·38, 0·96; P=0·033, P for trend=0·039). In contrast, this same LSCRS was associated with a higher odds of EDS (Q_4 *v.* Q_1: OR 1·83, 95 % CI 1·07, 3·12; P=0·026, P for trend=0·047).

Moreover, a number of non-linear associations were also noted whereby a LSCRS was either inversely or positively associated with an outcome of interest when comparing one quartile with Q_1, but not with others. For instance, a lower lutein+zeaxanthin gene risk score was associated with a lower odds of TAG dyslipidaemia only when comparing Q_2 with Q_1 (OR 0·51, 95 % CI 0·31, 0·83; P=0·007). Thus, only the middle part of the distribution for lower lutein+zeaxanthin status was linked to the reduced odds of this type of dyslipidaemia, whereas the remaining part of the distribution (Q_3 and Q_4) showed a comparable odds of this outcome with Q_1. Similarly, a lower odds of EDS was found when comparing Q_2 with Q_1 of the low α-carotene gene score, but not with others. In contrast, a gene score reflecting a low lycopene level was associated with a higher risk of central obesity only when comparing Q_2 with Q_1 (OR 2·81, 95 % CI 1·09, 7·26; P=0·033), with the association weakening with each higher quartile comparison. Importantly, the lutein+zeaxanthin LSCRS was inversely related to the odds of having NCEP ATP III MetS, though only for Q_2 and Q_3 *v.* Q_1, without a significant linear trend being observed.

As detailed in Table 4, the associations of the LTCRS with metabolic outcomes and EDS were assessed by a series of multiple logistic regression, using quartiles of the risk score as the main predictor and testing for linear trend in the association. Among the key findings, an inverse and linear association between the LTCRS and HDL-C dyslipidaemia indicated that a gene score associated with low carotenoid status was potentially protective against this outcome (Q_4 *v.* Q_1: OR 0·67, 95 % CI 0·45, 0·99; P=0·046, P for trend=0·046). Similarly, a non-linear association was found for elevated CRP (Q_2 *v.* Q_1: OR 0·63, 95 % CI 0·43, 0·91; P=0·015).

Discussion

In the present study, we examined the associations of gene polymorphisms related to low carotenoid status with various metabolic outcomes and EDS in an urban, socio-economically diverse sample of African-American adults. None of the key findings for SNP analyses survived correction for multiple testing. However, an inverse association was found between the LTCRS and HDL-C dyslipidaemia. The β-cryptoxanthin LSCRS was associated with a lower odds of HDL-C dyslipidaemia, but a higher odds of EDS.

Previous studies that examined SNP used in our SNPlcar focused on dyslipidaemia, type 2 diabetes, obesity and the MetS.

British Journal of Nutrition

Table 2. Gene SNP related to low carotenoid status (SNPlcar) and their associations with selected binary metabolic outcomes (obesity, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) metabolic syndrome (MetS)) and elevated depressive symptoms (EDS) among African-American adults assessed by multiple logistic regression analysis*

(Odds ratios and 95 % confidence intervals)

	Gene	OR	95 % CI	*P*
Obesity (*n* 990)				
SNPlcar$_1$: rs6720173:C/G (0,1,2)	*ABCG5*	0·86	0·70, 1·08	0·20
SNPlcar$_2$: rs934197:T/C (0,1,2)	*ApoB*	0·91	0·66, 1·25	0·56
SNPlcar$_3$: rs675:TT = 1 *v.* others = 0	*ApoA-IV*	0·97	0·70, 1·33	0·84
SNPlcar$_4$: apoE3/2 = 2 *v.* E3/3 = 0, others = 1	*ApoE*	0·94	0·77, 1·14	0·54
SNPlcar$_5$: rs6564851:T/G (0,1,2)	*BCMO1*	1·10	0·91, 1·34	0·32
SNPlcar$_6$: rs6564851:T/G (2,1,0)	*BCMO1*	0·90	0·75, 1·10	0·32
SNPlcar$_7$: rs12934922:T/A (2,1,0) + rs7501331:T/C (2,1,0)	*BCMO1*	1·04	0·79, 1·35	0·79
SNPlcar$_8$: rs7501331:T/C (2,1,0)	*BCMO1*	0·83	0·50, 1·37	0·47
SNPlcar$_9$: rs56389940:A/C (0,1,2)	*BCMO1*	0·84	0·63, 1·14	0·27
SNPlcar$_{10}$: rs12918164:A/G (0,1,2)	*BCMO1*	1·04	0·61, 1·76	0·88
SNPlcar$_{11}$: rs10048138:A/G (0,1,2)	*BCMO1*	1·10	0·89, 1·35	0·35
SNPlcar$_{12}$: rs4889293:G/C (0,1,2)	*BCMO1*	1·20	0·92, 1·56	0·17
SNPlcar$_{13}$: rs12934922:T/A (0,1,2)	*BCMO1*	0·89	0·67, 1·20	0·46
SNPlcar$_{14}$: rs4448930:C/G (0,1,2)	*BCMO1*	0·83	0·57, 1·19	0·31
SNPlcar$_{15}$: rs1165428:A/G (2,1,0)	*BCMO1*	1·18	0·88, 1·60	0·27
SNPlcar$_{16}$: rs6420424:G/A (2,1,0)	*BCMO1*	1·20	0·99, 1·46	0·06
SNPlcar$_{17}$: rs8044334:G/T (0,1,2)	*BCMO1*	0·80	0·67, 0·98	0·028
SNPlcar$_{18}$: rs1761667:A/G (2,1,0)	*CD36*	0·92	0·76, 1·12	0·40
SNPlcar$_{19}$: rs13230419:T/C: CC = 1 *v.* others = 0	*CD36*	1·03	0·76, 1·39	0·85
SNPlcar$_{20}$: rs1800588:T/C: TT = 1 *v.* others = 0	*LIPC*	0·82	0·60, 1·11	0·20
SNPlcar$_{21}$: rs1800588:T/C (0,1,2)	*LIPC*	1·13	0·93, 1·37	0·21
SNPlcar$_{22}$: rs1799883:A/G: GG = 1 *v.* others = 0	*FABP2*	3·41	0·88, 13·13	0·07
SNPlcar$_{23}$: rs328:G/C (2,1,0)	*LPL*	0·75	0·51, 1·12	0·16
SNPlcar$_{24}$: rs61932577:A/G: GG = 1 *v.* others = 0	*SCARB1*	2·40	1·03, 5·61	0·043
NCEP ATP III MetS (*n* 928)				
SNPlcar$_1$: rs6720173:C/G (0,1,2)	*ABCG5*	0·97	0·77, 1·23	0·81
SNPlcar$_2$: rs934197:T/C (0,1,2)	*ApoB*	0·72	0·52, 1·00	0·048
SNPlcar$_3$: rs675:TT = 1 *v.* others = 0	*ApoA-IV*	0·95	0·67, 1·35	0·77
SNPlcar$_4$: apoE3/2 = 2 *v.* E3/3 = 0, others = 1	*ApoE*	0·99	0·80, 1·23	0·94
SNPlcar$_5$: rs6564851:T/G (0,1,2)	*BCMO1*	0·97	0·78, 1·20	0·76
SNPlcar$_6$: rs6564851:T/G (2,1,0)	*BCMO1*	1·03	0·83, 1·28	0·76
SNPlcar$_7$: rs12934922:T/A (2,1,0) + rs7501331:T/C (2,1,0)	*BCMO1*	0·95	0·71, 1·28	0·75
SNPlcar$_8$: rs7501331:T/C (2,1,0)	*BCMO1*	1·02	0·60, 1·74	0·94
SNPlcar$_9$: rs56389940:A/C (0,1,2)	*BCMO1*	0·88	0·64, 1·22	0·47
SNPlcar$_{10}$: rs12918164:A/G (0,1,2)	*BCMO1*	0·74	0·43, 1·29	0·29
SNPlcar$_{11}$: rs10048138:A/G (0,1,2)	*BCMO1*	0·86	0·69, 1·08	0·21
SNPlcar$_{12}$: rs4889293:G/C (0,1,2)	*BCMO1*	1·07	0·81, 1·43	0·62
SNPlcar$_{13}$: rs12934922:T/A (0,1,2)	*BCMO1*	1·07	0·77, 1·49	0·69
SNPlcar$_{14}$: rs4448930:C/G (0,1,2)	*BCMO1*	1·09	0·72, 1·65	0·69
SNPlcar$_{15}$: rs1165428:A/G (2,1,0)	*BCMO1*	1·13	0·81, 1·57	0·46
SNPlcar$_{16}$: rs6420424:G/A (2,1,0)	*BCMO1*	1·15	0·93, 1·42	0·20
SNPlcar$_{17}$: rs8044334:G/T (0,1,2)	*BCMO1*	1·03	0·84, 1·27	0·75
SNPlcar$_{18}$: rs1761667:A/G (2,1,0)	*CD36*	0·88	0·70, 1·10	0·27
SNPlcar$_{19}$: rs13230419:T/C: CC = 1 *v.* others = 0	*CD36*	0·93	0·67, 1·29	0·66
SNPlcar$_{20}$: rs1800588:T/C: TT = 1 *v.* others = 0	*LIPC*	0·92	0·66, 1·29	0·64
SNPlcar$_{21}$: rs1800588:T/C (0,1,2)	*LIPC*	1·02	0·83, 1·27	0·83
SNPlcar$_{22}$: rs1799883:A/G: GG = 1 *v.* others = 0	*FABP2*	0·39	0·13, 1·18	0·10
SNPlcar$_{23}$: rs328:G/C (2,1,0)	*LPL*	0·58	0·36, 0·92	0·022
SNPlcar$_{24}$: rs61932577:A/G: GG = 1 *v.* others = 0	*SCARB1*	0·55	0·25, 1·20	0·13
EDS, CES-D score ≥16 (*n* 873)				
SNPlcar$_1$: rs6720173:C/G (0,1,2)	*ABCG5*	0·96	0·75, 1·23	0·73
SNPlcar$_2$: rs934197:T/C (0,1,2)	*ApoB*	0·86	0·61, 1·23	0·41
SNPlcar$_3$: rs675:TT = 1 *v.* others = 0	*ApoA-IV*	1·30	0·89, 1·90	0·18
SNPlcar$_4$: apoE3/2 = 2 *v.* E3/3 = 0, others = 1	*ApoE*	0·94	0·75, 1·18	0·60
SNPlcar$_5$: rs6564851:T/G (0,1,2)	*BCMO1*	0·95	0·76, 1·18	0·63
SNPlcar$_6$: rs6564851:T/G (2,1,0)	*BCMO1*	1·06	0·84, 1·32	0·63
SNPlcar$_7$: rs12934922:T/A (2,1,0) + rs7501331:T/C (2,1,0)	*BCMO1*	1·03	0·77, 1·38	0·83
SNPlcar$_8$: rs7501331:T/C (2,1,0)	*BCMO1*	1·14	0·67, 1·92	0·64
SNPlcar$_9$: rs56389940:A/C (0,1,2)	*BCMO1*	1·39	1·00, 1·94	0·05
SNPlcar$_{10}$: rs12918164:A/G (0,1,2)	*BCMO1*	1·49	0·77, 2·89	0·24
SNPlcar$_{11}$: rs10048138:A/G (0,1,2)	*BCMO1*	1·02	0·81, 1·30	0·83
SNPlcar$_{12}$: rs4889293:G/C (0,1,2)	*BCMO1*	0·77	0·58, 1·03	0·08
SNPlcar$_{13}$: rs12934922:T/A (0,1,2)	*BCMO1*	1·00	0·72, 1·42	0·96
SNPlcar$_{14}$: rs4448930:C/G (0,1,2)	*BCMO1*	2·05	1·27, 3·31	0·003

Table 2. *Continued*

	Gene	OR	95 % CI	*P*
$SNPlcar_{15}$: rs1165428:A/G (2,1,0)	*BCMO1*	0·72	0·51, 1·00	0·05
$SNPlcar_{16}$: rs6420424:G/A (2,1,0)	*BCMO1*	1·07	0·86, 1·34	0·52
$SNPlcar_{17}$: rs8044334:G/T (0,1,2)	*BCMO1*	0·95	0·76, 1·18	0·64
$SNPlcar_{18}$: rs1761667:A/G (2,1,0)	*CD36*	0·90	0·71, 1·14	0·40
$SNPlcar_{19}$: rs13230419:T/C: CC = 1 *v.* others = 0	*CD36*	1·41	0·99, 2·00	0·06
$SNPlcar_{20}$: rs1800588:T/C: TT = 1 *v.* others = 0	*LIPC*	1·04	0·74, 1·47	0·81
$SNPlcar_{21}$: rs1800588:T/C (0,1,2)	*LIPC*	0·93	0·74, 1·16	0·54
$SNPlcar_{22}$: rs1799883:A/G: GG = 1 *v.* others = 0	*FABP2*	2·44	0·30, 20·1	0·41
$SNPlcar_{23}$: rs328:G/C (2,1,0)	*LPL*	1·12	0·74, 1·71	0·60
$SNPlcar_{24}$: rs61932577:A/G: GG = 1 *v.* others = 0	*SCARB1*	1·72	0·60, 4·97	0·32

ABCG5, ATP-binding cassette, subfamily G, member 5; *BCMO1*, β-carotene mono-oxygenase 1; *CD36*, thrombospondin receptor; *LIPC*, hepatic lipase; *FABP2*, fatty acid-binding protein 2; *LPL*, lipoprotein lipase; *SCARB1*, scavenger receptor class B member 1; CES-D, Center for Epidemiologic Studies-Depression.

* Each SNPlcar was entered in a separate multiple logistic regression model as the main predictor. SNP allele dosage was coded as is or reverse coded (0,1,2 or 2,1,0) depending on whether the minor allele was associated with lower carotenoid status or vice versa (for details, see online supplementary Table S1). Covariates entered as potential confounders included sex, age, poverty income ratio (<125 *v.* ≥125 %), education (below high school, high school or above high school), marital status (current, former, never or missing), smoking status (current, former, never or missing), drug use (current, past, never or missing) and ten principal components to adjust for population structure.

Particularly, $SNPlcar_{1(ABCG5,rs6720173:C/G,lutein+zeaxanthin)}$ [21,22] has been found to be unrelated to HDL-C dyslipidaemia or other lipids based on a study of Puerto Rican adults, while other associations were found for various other SNP studied on that gene locus [45]. The main function of ABCG5 (ATP-binding cassette, subfamily G, member 5) is to translocate various hydrophobic substrates including carotenoids and cholesterol across extra- and intracellular membranes[21].

Moreover, only a few studies directly examined the associations of $SNPlcar_{2(ApoB\text{-}516,\beta\text{-carotene})}$ [22,23] with lipid profile and other metabolic disturbances. In one study[46], while another *ApoB* SNP (rs676210) has been reported to be associated with the lowering of TAG, $SNPlcar_2$ (rs934197:T/C) has not been found to be associated, a finding replicated by at least one other study[47]. However, two recent studies have detected an association of the 'T' allele dosage of that SNP with a higher postprandial TAG level[48] and increased insulin resistance[49]. In the present study, before correction for multiple testing (see Table 2 and online supplementary Table S2), the *ApoB*-516 'C' allele dosage ($SNPlcar_{2(ApoB)}$) yielded an inverse association with the MetS (OR 0·72, 95 % CI 0·52, 1·00; $P=0·048$) and elevated CRP (OR 0·70, 95 % CI 0·51, 0·95; $P=0·022$), which is consistent with previous studies. However, this finding was against the hypothesised direction that genetic polymorphisms linked to lower carotenoid status would be related to a higher odds of metabolic outcomes and EDS. ApoB is essential for the assembly and secretion of chylomicra and/or VLDL in the small intestine and the liver. It is also the main apo of LDL-C, a major carrier of carotenoids and TAG-rich lipoproteins[50].

The main function of ApoA-IV is lipid absorption and modifying lipoprotein size[51]. Although no associations were detected in the present study with $SNPlcar_3$ (*ApoA-IV*, rs675:A/T), previously linked to lower serum lycopene[22,23], other studies have shown that this SNP was associated with the ability of fenofibrate to lower TAG levels among non-MetS patients[52].

Moreover, in that same study[52], one of the *ApoE* SNP included in $SNPlcar_4$ (rs429358:C/T) was associated with increased LDL-C levels after fenofibrate treatment in the MetS group. *ApoE2* has been reported to have established atheroprotective properties based on previous studies (e.g. Morabia *et al.*[53]). However, we did not detect significant associations between $SNPlcar_{4(ApoE)}$ and any of the outcomes studied.

BCMO1 and BCDO2 are involved in symmetric and asymmetric carotenoid cleavage, respectively, and convert β-carotene and apocarotenals to retinal, thus influencing the circulatory levels of carotenoids[54]. For two of the most highly studied SNP in the *BCMO1* gene ($SNPlcar_5$: rs6564851:G/T and $SNPlcar_6$: rs6564851:T/G), with $SNPlcar_{5(BCMO1,lutein+zeaxanthin)}$ and $SNPlcar_{6(BCMO1,\beta\text{-cryptoxanthin})}$, no relationship was observed with metabolic outcomes or EDS, in accordance with a meta-analysis suggesting that the loss of *BCMO1* function was unrelated to a higher risk of type 2 diabetes[55]. Moreover, in a recent French-Canadian study[56], it has been demonstrated that $SNPlcar_{7(BCMO1,\beta\text{-carotene})}$ and $SNPlcar_{13(BCMO1,\beta\text{-carotene})}$ [28] had no association with a lower HDL-C level. No other SNPlcar on the *BCMO1* gene locus have previously been studied in relation to metabolic disturbance or depressive symptoms. In the present study, although none of the associations remained significant after correction for multiple testing, among the notable associations before that correction, $SNPlcar_{14(BCMO1,\beta\text{-cryptoxanthin})}$ [28] was associated with a higher odds of EDS (OR 2·05, 95 % CI 1·27, 3·31; $P=0·003$; Table 2). Other associations detected were either in the expected direction ($SNPlcar_{12(BCMO1,\alpha\text{-carotene})}$ and central obesity; $SNPlcar_{14(BCMO1,\beta\text{-cryptoxanthin})}$ and $SNPlcar_{16(BCMO1,\beta\text{-carotene})}$ with hypertension) or against the hypothesised direction ($SNPlcar_{17(BCMO1,\beta\text{-carotene})}$ and obesity; $SNPlcar_{10(BCMO1,\beta\text{-cryptoxanthin})}$ and hypertension). Thus, further larger studies are needed to reconcile those inconsistent findings within that gene locus.

$SNPlcar_{19(CD36,lutein+zeaxanthin)}$ (thrombospondin receptor gene (rs13230419)) has been shown to increase the odds of the MetS by 29–40 % in the African-American population[57]. *CD36* codes for a membrane protein that facilitates the uptake and utilisation of fatty acids in key metabolic tissues. The present study found a similar putative effect, though there was only a significant or marginally significant association with the MetS before correction for multiple testing

Table 3. Low specific-carotenoid risk scores (LSCRS, quartiles (Q)) and their associations with selected binary metabolic outcomes (central obesity, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) metabolic syndrome (MetS) and its components, elevated homeostatic model assessment-insulin resistance (HOMA-IR), elevated C-reactive protein (CRP) and hyperuricaemia) and elevated depressive symptoms (EDS) among African-American adults assessed by multiple logistic regression analysis*

(Odds ratios and 95 % confidence intervals)

		Q2			Q3			Q4			
	Q1	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	*P* for trend
Obesity (*n* 990)											
α-Carotene	1	0·93	0·63, 1·37	0·70	0·93	0·63, 1·36	0·70	0·87	0·59, 1·28	0·49	0·60
β-Carotene	1	0·82	0·55, 1·23	0·34	1·06	0·72, 1·56	0·77	0·88	0·59, 1·32	0·55	0·92
Lutein+zeaxanthin	1	0·88	0·59, 1·31	0·53	0·92	0·61, 1·41	0·72	0·85	0·55, 1·31	0·46	0·59
β-Cryptoxanthin	1	1·00	0·66, 1·47	0·96	0·80	0·53, 1·22	0·30	0·90	0·58, 1·40	0·65	0·44
Lycopene	1	1·99	0·86, 4·61	0·11	1·32	0·73, 2·36	0·46	1·25	0·70, 2·22	0·46	0·95
Central obesity (*n* 957)											
α-Carotene	1	1·09	0·71, 1·68	0·68	1·34	0·87, 2·06	0·19	0·97	0·64, 1·49	0·90	0·79
β-Carotene	1	0·80	0·51, 1·24	0·32	1·39	0·89, 2·15	0·14	1·01	0·64, 1·57	0·97	0·50
Lutein+zeaxanthin	1	0·92	0·59, 1·44	0·72	0·96	0·60, 1·54	0·88	0·74	0·45, 1·21	0·23	0·37
β-Cryptoxanthin	1	0·92	0·59, 1·43	0·72	1·19	0·75, 1·89	0·46	0·97	0·59, 1·60	0·92	0·93
Lycopene	1	2·81	1·09, 7·26	0·033	1·80	0·95, 3·42	0·07	1·36	0·72, 2·57	0·34	0·70
NCEP ATP III MetS (*n* 928)											
α-Carotene	1	0·74	0·48, 1·14	0·17	0·77	0·50, 1·18	0·22	0·81	0·53, 1·23	0·32	0·38
β-Carotene	1	1·07	0·68, 1·69	0·76	1·34	0·87, 2·06	0·19	1·18	0·75, 1·86	0·47	0·30
Lutein+zeaxanthin	1	0·58	0·37, 0·90	0·014	0·52	0·33, 0·84	0·007	0·69	0·43, 1·11	0·13	0·13
β-Cryptoxanthin	1	0·96	0·62, 1·50	0·87	0·96	0·60, 1·53	0·87	0·84	0·51, 1·38	0·50	0·67
Lycopene	1	1·79	0·74, 4·35	0·20	1·17	0·63, 2·19	0·61	0·82	0·51, 1·38	0·50	0·06
Elevated blood pressure (*n* 977)											
α-Carotene	1	1·36	0·92, 2·03	0·12	1·05	0·71, 1·57	0·79	0·97	0·65, 1·46	0·90	0·58
β-Carotene	1	1·30	0·87, 1·95	0·21	1·13	0·76, 1·69	0·55	1·21	0·80, 1·83	0·37	0·61
Lutein+zeaxanthin	1	0·79	0·53, 1·19	0·26	0·68	0·44, 1·04	0·08	0·84	0·54, 1·31	0·45	0·30
β-Cryptoxanthin	1	1·06	0·71, 1·59	0·78	0·96	0·62, 1·47	0·86	0·74	0·42, 1·33	0·32	0·97
Lycopene	1	0·90	0·39, 2·09	0·82	0·96	0·54, 1·71	0·90	0·75	0·42, 1·33	0·32	0·12
Dyslipidaemia, HDL-C (*n* 989)											
α-Carotene	1	0·71	0·47, 1·06	0·09	0·68	0·45, 1·01	0·06	0·65	0·44, 0·97	0·037	0·045
β-Carotene	1	0·91	0·60, 1·39	0·68	1·23	0·82, 1·83	0·32	1·02	0·67, 1·54	0·93	0·51
Lutein+zeaxanthin	1	0·73	0·48, 1·10	0·13	0·65	0·42, 1·00	0·05	0·80	0·51, 1·25	0·32	0·34
β-Cryptoxanthin	1	0·82	0·54, 1·24	0·34	0·70	0·46, 1·07	0·10	0·61	0·38, 0·96	0·033	0·039
Lycopene	1	1·06	0·45, 2·48	0·89	0·89	0·50, 1·60	0·70	0·75	0·42, 1·34	0·33	0·14
Dyslipidaemia, TAG (*n* 989)											
α-Carotene	1	1·21	0·76, 1·91	0·43	0·69	0·42, 1·15	0·16	1·01	0·63, 1·62	0·96	0·48
β-Carotene	1	1·02	0·62, 1·69	0·93	1·06	0·65, 1·73	0·82	1·11	0·68, 1·83	0·67	0·71
Lutein+zeaxanthin	1	0·51	0·31, 0·83	0·007	0·68	0·41, 1·12	0·13	0·80	0·47, 1·35	0·40	0·39
β-Cryptoxanthin	1	0·78	0·47, 1·28	0·33	0·95	0·57, 1·57	0·83	0·83	0·48, 1·44	0·51	0·63
Lycopene	1	2·02	0·72, 5·65	0·18	1·80	0·84, 3·89	0·13	1·26	0·59, 2·75	0·55	0·52
Hyperglycaemia (*n* 989)											
α-Carotene	1	0·83	0·55, 1·24	0·35	0·85	0·57, 1·27	0·43	1·06	0·71, 1·57	0·78	0·84
β-Carotene	1	1·22	0·82, 1·83	0·33	1·13	0·76, 1·69	0·61	0·94	0·62, 1·42	0·76	0·68
Lutein+zeaxanthin	1	0·80	0·54, 1·19	0·28	0·65	0·42, 1·00	0·05	0·88	0·56, 1·37	0·56	0·39
β-Cryptoxanthin	1	0·84	0·56, 1·26	0·39	0·84	0·55, 1·28	0·43	0·83	0·53, 1·30	0·42	0·61
Lycopene	1	2·16	0·91, 5·13	0·08	1·65	0·87, 3·06	0·12	1·39	0·75, 2·57	0·30	0·92
Elevated HOMA-IR (*n* 986)											
α-Carotene	1	0·87	0·59, 1·27	0·47	0·81	0·55, 1·18	0·27	1·00	0·69, 1·47	0·97	0·94
β-Carotene	1	0·91	0·62, 1·34	0·62	1·07	0·73, 1·56	0·75	0·78	0·52, 1·16	0·21	0·35
Lutein+zeaxanthin	1	0·81	0·55, 1·19	0·28	0·84	0·56, 1·27	0·41	0·95	0·62, 1·46	0·83	0·85
β-Cryptoxanthin	1	1·19	0·80, 1·76	0·40	1·35	0·90, 2·03	0·15	1·33	0·86, 2·05	0·21	0·15
Lycopene	1	1·91	0·83, 4·41	0·13	1·65	0·92, 2·97	0·10	1·56	0·87, 2·79	0·14	0·46
Elevated CRP (*n* 963)											
α-Carotene	1	0·98	0·67, 1·43	0·91	0·84	0·57, 1·23	0·37	1·06	0·72, 1·55	0·76	0·92
β-Carotene	1	1·27	0·86, 1·87	0·23	1·33	0·91, 1·95	0·14	0·92	0·62, 1·36	0·67	0·72
Lutein+zeaxanthin	1	0·95	0·65, 1·41	0·81	0·99	0·67, 1·50	0·97	0·81	0·53, 1·25	0·35	0·35
β-Cryptoxanthin	1	1·00	0·68, 1·48	0·99	1·02	0·68, 1·53	0·92	0·94	0·61, 1·44	0·76	0·84
Lycopene	1	0·97	0·42, 2·25	0·94	0·78	0·44, 1·36	0·38	0·69	0·39, 1·20	0·19	0·12
Hyperuricaemia (*n* 989)											
α-Carotene	1	0·64	0·41, 0·98	0·040	0·66	0·43, 1·02	0·06	0·89	0·58, 1·34	0·57	0·51
β-Carotene	1	1·11	0·71, 1·74	0·63	1·24	0·80, 1·93	0·33	1·12	0·71, 1·77	0·61	0·46
Lutein+zeaxanthin	1	0·79	0·51, 1·23	0·30	1·01	0·64, 1·59	0·98	0·91	0·56, 1·48	0·72	0·89
β-Cryptoxanthin	1	0·75	0·48, 1·17	0·20	0·85	0·54, 1·33	0·47	0·77	0·47, 1·25	0·29	0·44
Lycopene	1	1·35	0·53, 3·44	0·53	1·35	0·71, 2·56	0·36	1·02	0·53, 1·94	0·96	0·50
EDS, CES-D score ≥16 (*n* 873)											
α-Carotene	1	0·61	0·38, 0·96	0·034	0·80	0·50, 1·23	0·30	0·71	0·46, 1·11	0·14	0·31
β-Carotene	1	1·14	0·71, 1·82	0·58	0·98	0·62, 1·54	0·92	0·93	0·58, 1·48	0·76	0·65
Lutein+zeaxanthin	1	0·98	0·61, 1·56	0·89	1·04	0·63, 1·72	0·89	1·52	0·92, 2·54	0·10	0·11

Table 3. *Continued*

	Q1	Q2			Q3			Q4			
		OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	*P* for trend
β-Cryptoxanthin	1	1·68	1·05, 2·70	0·031	1·31	0·80, 2·14	0·28	1·83	1·07, 3·12	0·026	0·047
Lycopene	1	1·50	0·60, 3·75	0·39	0·80	0·41, 1·57	0·52	0·85	0·44, 1·66	0·64	0·37

HDL-C, HDL-cholesterol; CES-D, Center for Epidemiologic Studies-Depression.

* All LSCRS were entered in the same multiple logistic regression model (as quartiles, with the first quartile being the reference category) as main predictors, to assess their net association with each of the metabolic outcomes and with EDS. Covariates entered as potential confounders were sex, age, poverty income ratio (<125 *v.* ≥125 %), education (below high school, high school or above high school), marital status (current, former, never or missing), smoking status (current, former, never or missing), drug use (current, past, never or missing) and ten principal components to adjust for population structure.

(OR 1·41, 95 % CI 0·99, 2·00; *P*=0·06) and TAG dyslipidaemia (OR 0·66, 95 % CI 0·46, 0·94; *P*=0·021). In contrast, the present study did not find any significant associations with $SNPlcar_{18}$. $SNPlcar_{18(CD36,\text{low lutein + zeaxanthin with more 'A' alleles})}$[22,58] was related to the MetS in one previous case–control study of Egyptian adults, with the 'G' allele being more prevalent in cases (*n* 100) than in controls (*n* 100)[59]. A similar finding was observed in another study of 317 African-American adults, in which the 'A' allele of *CD36* (rs1761667:A/G) was associated with greater perceived creaminess regardless of the fat content of salad dressings (*P*<0·01) and a higher mean acceptance of added fats and oils (*P*=0·02) without a significant association with the obesity phenotype[60].

Hepatic lipase (LIPC) hydrolyses TAG and phospholipids from HDL, intermediate-density lipoproteins and LDL, transforming them into smaller and denser particles, and promoting the cellular uptake of HDL-C[61]. For the two *LIPC* gene SNPlcar (both rs1800588:T/C), $SNPlcar_{20}$ (TT *v.* others) has been previously shown to be associated with a low α-carotene level, while $SNPlcar_{21}$ (C allele) has been linked to a low β-carotene level[22,61]. A study conducted among a large cohort of Chinese adults (*n* 4194) has shown that the 'T' allele was linked to a higher HDL-C level than the 'C' allele (*P*<0·0001)[62]. The same pattern has been found in a large cohort study of Caucasian adults (*n* 4662), with the 'C' allele being associated with HDL-C dyslipidaemia (*P*<0·0001)[63]. The present study failed to detect an association between *LIPC* SNPlcar and various outcomes of interest.

Fatty acid-binding protein 2 (*FABP2*)-related $SNPlcar_{22}$ (rs1799883:A/G, GG *v.* others) was previously associated with a lower serum lycopene level[22,29]. In a study of 315 elderly subjects with the MetS who were of European descent, the 'G' allele was linked to lower TAG and higher HDL-C levels (*P*<0·05), indicative of lower risk for dyslipidaemia of both types[64]. There were no notable associations between this polymorphism and any of the outcomes of interest investigated in the present study. FABP2 is an intracellular protein expressed only in the intestine, which is involved in the absorption and intracellular transport of dietary long-chain fatty acids and carotenoids to their specific metabolic targets[61].

For lipoprotein lipase (*LPL*)-related $SNPlcar_{23}$ (rs328:G/C; GG *v.* CC, mainly low α-carotene level[22,30]), two previous studies conducted among Caucasian adults also indicated that the 'C' allele was consistently linked to HDL-C dyslipidaemia[63,65], with one of them observing an additional link to TAG dyslipidaemia[65]. However, a recent meta-analysis showed only a modest relationship between rs328:G/C and both types of dyslipidaemia[66]. Before correction for multiple

Table 4. Low total-carotenoid risk scores (LTCRS, quartiles (Q)) and their associations with selected binary metabolic outcomes (central obesity, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) metabolic syndrome (MetS) and its components, elevated homeostatic model assessment, insulin resistance (HOMA-IR), elevated C-reactive protein (CRP) and hyperuricaemia) and elevated depressive symptoms (EDS) among African-American adults assessed by multiple logistic regression analysis*

(Odds ratios and 95 % confidence intervals)

	Q1	Q2			Q3			Q4			
		OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	*P* for trend
Obesity	1	0·86	0·58, 1·26	0·44	1·11	0·76, 1·63	0·59	0·80	0·54, 1·17	0·25	0·50
Central obesity	1	0·85	0·56, 1·30	0·45	1·01	0·66, 1·55	0·96	0·83	0·54, 1·27	0·38	0·56
NCEP ATP III MetS	1	0·87	0·57, 1·32	0·51	0·71	0·45, 1·09	0·12	0·68	0·44, 1·05	0·08	0·05
Elevated blood pressure	1	0·86	0·59, 1·27	0·46	0·70	0·48, 1·04	0·08	0·88	0·59, 1·30	0·52	0·34
Dyslipidaemia, HDL-C	1	0·80	0·54, 1·19	0·28	0·76	0·51, 1·12	0·17	0·67	0·45, 0·99	0·046	0·046
Dyslipidaemia, TAG	1	1·28	0·81, 2·02	0·29	0·91	0·56, 1·46	0·69	0·79	0·48, 1·29	0·35	0·18
Hyperglycaemia	1	0·93	0·63, 1·38	0·71	1·14	0·76, 1·69	0·50	0·93	0·62, 1·39	0·73	0·99
Elevated HOMA-IR	1	0·90	0·61, 1·32	0·59	1·25	0·86, 1·81	0·24	0·82	0·56, 1·22	0·34	0·73
Elevated CRP	1	0·63	0·43, 0·91	0·015	0·75	0·52, 1·10	0·14	0·79	0·54, 1·16	0·23	0·41
Hyperuricaemia	1	1·17	0·77, 1·78	0·45	0·92	0·60, 1·42	0·71	0·92	0·60, 1·43	0·72	0·48
EDS, CES-D score ≥16	1	1·10	0·71, 1·74	0·65	1·25	0·80, 1·97	0·33	1·16	0·74, 1·82	0·52	0·45

HDL-C, HDL-cholesterol; CES-D, Center for Epidemiologic Studies-Depression.

* The LTCRS was entered in the multiple logistic regression model (as quartiles, with the first quartile being the reference category) as main predictors, to assess their net association with each of the metabolic outcomes and with EDS. Covariates entered as potential confounders were sex, age, poverty income ratio (<125 *v.* ≥125 %), education (below high school, high school or above high school), marital status (current, former, never or missing), smoking status (current, former, never or missing), drug use (current, past, never or missing) and ten principal components to adjust for population structure.

testing, the present study was indicative of a consistent relationship in which the 'G' allele was associated with a lower odds of elevated HOMA-IR (OR 0·66, 95 % CI 0·44, 0·98; $P=0·037$; see online supplementary Table S3). However, this SNPlcar was not found to be associated with any type of dyslipidaemia in the present study. LPL catalyses the hydrolysis of the TAG component of circulating chylomicrons and VLDL, in tissues other than the liver, and indirectly affects the concentration of carotenoids[30].

SCARB1 SNPlcar$_{24}$ (SR-BI exon 1, rs61932577:A/G; GG *v.* others), previously linked to a lower level of β-cryptoxanthin[22,23], was also studied in relation to lipid profiles among adults. SRBI has been shown to play a role in the metabolism of ApoB-containing lipoproteins in animal models and human subjects. In fact, SRBI constitutes a back-up pathway to the usual LDL receptor-mediated pathways for the catabolism of these lipoproteins. This is particularly relevant to adults with high ApoB-containing lipoproteins, commonly occurring in patients with familial hypercholesterolaemia[67]. Before correction for multiple testing, the present study found that SNPlcar$_{24(SCARB1)}$ (i.e. higher 'G' allele dosage) was linked to a higher odds of obesity, but no association was found with HDL-C or TAG dyslipidaemia. The associations of *SCARB1* with HDL-C and TAG dyslipidaemia were investigated previously, with a higher dosage of the 'A' allele being related to higher HDL-C and lower LDL-C values in men, but not in women[68]. This finding was replicated in a large study of US Caucasians (Framingham study: 2463 non-diabetic and 187 diabetic), in which diabetic subjects with the less common allele (allele A) had lower lipid concentrations, particularly LDL-C[69]. Those two studies had a consistent pattern of association found in the present study, though with different outcomes. However, two other studies found no associations of this SNPlcar with various lipid parameters[53,70]. Inconsistent with the pattern of findings from the present study and those of others, a study of seventy-seven subjects who were heterozygous for familial hypercholesterolaemia has found that the 'A' allele dosage of this SNP was associated with higher TAG[67].

To our knowledge, the present study is the first to systematically examine genetic polymorphisms previously shown to be associated with the lower levels of serum carotenoids in relation to metabolic disturbance and depressive symptoms in an urban population of African-American adults, and to construct gene scores for that purpose. Despite its strengths, some limitations include a statistical power-limiting small sample size. Moreover, most GWAS yielding our SNPlcar short list came from studies of subjects of European ancestry. Finally, data on serum carotenoid concentrations were lacking, which prevented the direct assessment of SNPlcar associations with respective carotenoids and comparisons with previous studies of European ancestry subjects. Additionally, such data availability would have allowed the use of gene score weights depending on effect sizes of each SNPlcar on various carotenoids. Finally, in few gene loci included in of gene score computations, a SNP was related to multiple carotenoids, specifically *BCMO1*. However, to bypass this issue, the gene scores were made mutually exclusive by including only the most significant carotenoid for each of the carotenoid-specific gene score.

In conclusion, gene polymorphisms linked to low serum carotenoid status had mixed effects on metabolic disturbance and depression. Specifically, our findings do not support that gene polymorphisms associated with low carotenoid status will necessarily lead to a poorer metabolic and depressive symptom outcome. In fact, in most cases, the opposite trend was found, with the possible exception of the β-cryptoxanthin risk score and EDS. Therefore, there is a major discrepancy between what was found in studies linking serum carotenoids to metabolic disturbance and depressive symptoms and the present study that used gene polymorphisms linked to low carotenoid status as the main exposure. It is possible that different carotenoids may interact either synergistically or antagonistically with each other to affect these outcomes. Thus, similar studies on larger African-American samples are needed to test gene–gene (epistasis) interactions between these carotenoid-related gene polymorphisms.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114514001706

Acknowledgements

The authors thank Dr Lori L. Beason-Held (NIA/NIH/IRP) for internally reviewing the manuscript and Dr Toshiko Tanaka (NIA/NIH/IRP) for additional help with the revision.

The present study was fully supported by the Intramural Research Program of the NIH, National Institute on Aging.

The contributions of the authors are as follows: M. A. B. had full access to the data, completed all the statistical analyses, wrote and revised the manuscript, planned the analysis, performed the data management and statistical analysis, and had primary responsibility for the final content; M. A. N. wrote and revised parts of the manuscript, participated in literature review, participated in data acquisition, plan of the analysis and statistical analysis; J. A. C. wrote and revised parts of the manuscript, and participated in literature review and plan of the analysis; M. K. E. wrote and revised parts of the manuscript and participated in data acquisition; A. B. Z. wrote and revised parts of the manuscript, and participated in data acquisition and plan of analysis. All authors read and approved the final version of the manuscript.

None of the authors has declared any conflict of interest.

References

1. Soory M (2009) Relevance of nutritional antioxidants in metabolic syndrome, ageing and cancer: potential for therapeutic targeting. *Infect Disord Drug Targets* **9**, 400–414.
2. Rao AV & Rao LG (2007) Carotenoids and human health. *Pharmacol Res* **55**, 207–216.
3. Voutilainen S, Nurmi T, Mursu J, *et al.* (2006) Carotenoids and cardiovascular health. *Am J Clin Nutr* **83**, 1265–1271.
4. Montonen J, Knekt P, Jarvinen R, *et al.* (2004) Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care* **27**, 362–366.

5. Coyne T, Ibiebele TI, Baade PD, *et al.* (2005) Diabetes mellitus and serum carotenoids: findings of a population-based study in Queensland, Australia. *Am J Clin Nutr* **82**, 685–693.
6. Ford ES, Will JC, Bowman BA, *et al.* (1999) Diabetes mellitus and serum carotenoids: findings from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* **149**, 168–176.
7. Hozawa A, Jacobs DR Jr, Steffes MW, *et al.* (2006) Associations of serum carotenoid concentrations with the development of diabetes and with insulin concentration: interaction with smoking: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol* **163**, 929–937.
8. Reunanen A, Knekt P, Aaran RK, *et al.* (1998) Serum antioxidants and risk of non-insulin dependent diabetes mellitus. *Eur J Clin Nutr* **52**, 89–93.
9. Ford ES, Mokdad AH, Giles WH, *et al.* (2003) The metabolic syndrome and antioxidant concentrations: findings from the Third National Health and Nutrition Examination Survey. *Diabetes* **52**, 2346–2352.
10. Beydoun MA, Shroff MR, Chen X, *et al.* (2011) Serum antioxidant status is associated with metabolic syndrome among U.S. adults in recent national surveys. *J Nutr* **141**, 903–913.
11. Beydoun MA, Canas JA, Beydoun HA, *et al.* (2012) Serum antioxidant concentrations and metabolic syndrome are associated among U.S. adolescents in recent national surveys. *J Nutr* **142**, 1693–1704.
12. Beydoun MA, Beydoun HA, Boueiz A, *et al.* (2013) Antioxidant status and its association with elevated depressive symptoms among US adults: National Health and Nutrition Examination Surveys 2005–6. *Br J Nutr* **109**, 1714–1729.
13. Milaneschi Y, Bandinelli S, Penninx BW, *et al.* (2012) The relationship between plasma carotenoids and depressive symptoms in older persons. *World J Biol Psychiatry* **13**, 588–598.
14. Kataja-Tuomola M, Sundell JR, Mannisto S, *et al.* (2008) Effect of alpha-tocopherol and beta-carotene supplementation on the incidence of type 2 diabetes. *Diabetologia* **51**, 47–53.
15. Liu S, Ajani U, Chae C, *et al.* (1999) Long-term beta-carotene supplementation and risk of type 2 diabetes mellitus: a randomized controlled trial. *JAMA* **282**, 1073–1075.
16. Wang L, Liu S, Pradhan AD, *et al.* (2006) Plasma lycopene, other carotenoids, and the risk of type 2 diabetes in women. *Am J Epidemiol* **164**, 576–585.
17. Wang L, Liu S, Manson JE, *et al.* (2006) The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. *J Nutr* **136**, 620–625.
18. Beydoun MA, Kuczmarski MT, Mason MA, *et al.* (2009) Role of depressive symptoms in explaining socioeconomic status disparities in dietary quality and central adiposity among US adults: a structural equation modeling approach. *Am J Clin Nutr* **90**, 1084–1095.
19. Kimura Y, Matsushita Y, Nanri A, *et al.* (2011) Metabolic syndrome and depressive symptoms among Japanese men and women. *Environ Health Prev Med* **16**, 363–368.
20. Akbaraly TN, Ancelin ML, Jaussent I, *et al.* (2011) Metabolic syndrome and onset of depressive symptoms in the elderly: findings from the three-city study. *Diabetes Care* **34**, 904–909.
21. Herron KL, McGrane MM, Waters D, *et al.* (2006) The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. *J Nutr* **136**, 1161–1165.
22. Borel P (2012) Genetic variations involved in interindividual variability in carotenoid status. *Mol Nutr Food Res* **56**, 228–240.
23. Borel P, Moussa M, Reboul E, *et al.* (2007) Human plasma levels of vitamin E and carotenoids are associated with genetic polymorphisms in genes involved in lipid metabolism. *J Nutr* **137**, 2653–2659.
24. Ortega H, Castilla P, Gomez-Coronado D, *et al.* (2005) Influence of apolipoprotein E genotype on fat-soluble plasma antioxidants in Spanish children. *Am J Clin Nutr* **81**, 624–632.
25. Purcell S, Neale B, Todd-Brown K, *et al.* (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559–575.
26. Epstein MP, Duren WL & Boehnke M (2000) Improved inference of relationship for pairs of individuals. *Am J Hum Genet* **67**, 1219–1231.
27. Pritchard JK, Stephens M & Donnelly P (2000) Inference of population structure using multilocus genotype data. *Genetics* **155**, 945–959.
28. Hendrickson SJ, Hazra A, Chen C, *et al.* (2012) β-Carotene 15,15′-monooxygenase 1 single nucleotide polymorphisms in relation to plasma carotenoid and retinol concentrations in women of European descent. *Am J Clin Nutr* **96**, 1379–1389.
29. Falush D, Stephens M & Pritchard JK (2003) Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. *Genetics* **164**, 1567–1587.
30. Herbeth B, Gueguen S, Leroy P, *et al.* (2007) The lipoprotein lipase serine 447 stop polymorphism is associated with altered serum carotenoid concentrations in the Stanislas Family Study. *J Am Coll Nutr* **26**, 655–662.
31. Evans MK, Lepkowski JM, Powe NR, *et al.* (2010) Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. *Ethn Dis* **20**, 267–275.
32. Lietz G, Oxley A, Leung W, *et al.* (2012) Single nucleotide polymorphisms upstream from the β-carotene 15,15′-monoxygenase gene influence provitamin A conversion efficiency in female volunteers. *J Nutr* **142**, 161S–165S.
33. Reich DE, Cargill M, Bolk S, *et al.* (2001) Linkage disequilibrium in the human genome. *Nature* **411**, 199–204.
34. Grimsby JL, Porneala BC, Vassy JL, *et al.* (2012) Race-ethnic differences in the association of genetic loci with HbA1c levels and mortality in U.S. adults: the Third National Health and Nutrition Examination Survey (NHANES III). *BMC Med Genet* **13**, 30.
35. Wallace TM, Levy JC & Matthews DR (2004) Use and abuse of HOMA modeling. *Diabetes Care* **27**, 1487–1495.
36. Matthews DR, Hosker JP, Rudenski AS, *et al.* (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419.
37. Anonymous (2003) *Handbook of Diagnostic Tests*, 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins.
38. Ridker PM, Cushman M, Stampfer MJ, *et al.* (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* **336**, 973–979.
39. National Institute of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), North American Association for the Study of Obesity (NAASO) (2000) *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, No. 00-4084. Bethesda, MD: NIH.
40. National Institute of Health (NIH) (2001) *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive*

Summary. NIH Publication No. 01-3670. Bethesda, MD: National Institute of Health.
41. Lezak MD, Howeison DB & Loring DW (2004) *Neuropsychological Assessment*, 4th ed. New York, NY: Oxford University Press.
42. Radloff L (1977) The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* **1**, 385–401.
43. Nguyen HT, Kitner-Triolo M, Evans MK, *et al.* (2004) Factorial invariance of the CES-D in low socioeconomic status African Americans compared with a nationally representative sample. *Psychiatry Res* **126**, 177–187.
44. STATA (2013) *Statistics/Data Analysis: Release 13.0.* College Station, TX: Stata Corporation.
45. Junyent M, Tucker KL, Smith CE, *et al.* (2009) The effects of ABCG5/G8 polymorphisms on plasma HDL cholesterol concentrations depend on smoking habit in the Boston Puerto Rican Health Study. *J Lipid Res* **50**, 565–573.
46. Wojczynski MK, Gao G, Borecki I, *et al.* (2010) Apolipoprotein B genetic variants modify the response to fenofibrate: a GOLDN study. *J Lipid Res* **51**, 3316–3323.
47. Perez-Martinez P, Perez-Jimenez F, Ordovas JM, *et al.* (2007) The APOB-516C/T polymorphism has no effect on lipid and apolipoprotein response following changes in dietary fat intake in a healthy population. *Nutr Metab Cardiovasc Dis* **17**, 224–229.
48. Perez-Martinez P, Perez-Jimenez F, Ordovas JM, *et al.* (2007) Postprandial lipemia is modified by the presence of the APOB-516C/T polymorphism in a healthy Caucasian population. *Lipids* **42**, 143–150.
49. Perez-Martinez P, Perez-Jimenez F, Ordovas JM, *et al.* (2007) The APOB-516C/T polymorphism is associated with differences in insulin sensitivity in healthy males during the consumption of diets with different fat content. *Br J Nutr* **97**, 622–627.
50. Hammoud A, Gastaldi M, Maillot M, *et al.* (2010) APOB-516 T allele homozygous subjects are unresponsive to dietary changes in a three-month primary intervention study targeted to reduce fat intake. *Genes Nutr* **5**, 29–37.
51. Weinberg RB, Gallagher JW, Fabritius MA, *et al.* (2012) ApoA-IV modulates the secretory trafficking of apoB and the size of triglyceride-rich lipoproteins. *J Lipid Res* **53**, 736–743.
52. Feitosa MF, An P, Ordovas JM, *et al.* (2011) Association of gene variants with lipid levels in response to fenofibrate is influenced by metabolic syndrome status. *Atherosclerosis* **215**, 435–439.
53. Morabia A, Cayanis E, Costanza MC, *et al.* (2003) Association of extreme blood lipid profile phenotypic variation with 11 reverse cholesterol transport genes and 10 non-genetic cardiovascular disease risk factors. *Hum Mol Genet* **12**, 2733–2743.
54. Ziouzenkova O, Orasanu G, Sukhova G, *et al.* (2007) Asymmetric cleavage of beta-carotene yields a transcriptional repressor of retinoid X receptor and peroxisome proliferator-activated receptor responses. *Mol Endocrinol* **21**, 77–88.
55. Perry JR, Ferrucci L, Bandinelli S, *et al.* (2009) Circulating beta-carotene levels and type 2 diabetes-cause or effect? *Diabetologia* **52**, 2117–2121.
56. Dastani Z, Pajukanta P, Marcil M, *et al.* (2010) Fine mapping and association studies of a high-density lipoprotein cholesterol linkage region on chromosome 16 in French-Canadian subjects. *Eur J Hum Genet* **18**, 342–347.
57. Love-Gregory L, Sherva R, Sun L, *et al.* (2008) Variants in the *CD36* gene associate with the metabolic syndrome and high--density lipoprotein cholesterol. *Hum Mol Genet* **17**, 1695–1704.
58. Borel P, de Edelenyi FS, Vincent-Baudry S, *et al.* (2011) Genetic variants in BCMO1 and CD36 are associated with plasma lutein concentrations and macular pigment optical density in humans. *Ann Med* **43**, 47–59.
59. Bayoumy NM, El-Shabrawi MM & Hassan HH (2012) Association of cluster of differentiation 36 gene variant rs1761667 (G > A) with metabolic syndrome in Egyptian adults. *Saudi Med J* **33**, 489–494.
60. Keller KL, Liang LC, Sakimura J, *et al.* (2012) Common variants in the *CD36* gene are associated with oral fat perception, fat preferences, and obesity in African Americans. *Obesity (Silver Spring)* **20**, 1066–1073.
61. Borel P, Moussa M, Reboul E, *et al.* (2009) Human fasting plasma concentrations of vitamin E and carotenoids, and their association with genetic variants in apo C-III, cholesteryl ester transfer protein, hepatic lipase, intestinal fatty acid binding protein and microsomal triacylglycerol transfer protein. *Br J Nutr* **101**, 680–687.
62. Liu Y, Zhou D, Zhang Z, *et al.* (2011) Effects of genetic variants on lipid parameters and dyslipidemia in a Chinese population. *J Lipid Res* **52**, 354–360.
63. Lu Y, Dolle ME, Imholz S, *et al.* (2008) Multiple genetic variants along candidate pathways influence plasma high-density lipoprotein cholesterol concentrations. *J Lipid Res* **49**, 2582–2589.
64. Turkovic LF, Pizent A, Dodig S, *et al.* (2012) *FABP2* gene polymorphism and metabolic syndrome in elderly people of Croatian descent. *Biochem Med (Zagreb)* **22**, 217–224.
65. Webster RJ, Warrington NM, Weedon MN, *et al.* (2009) The association of common genetic variants in the *APOA5, LPL* and *GCK* genes with longitudinal changes in metabolic and cardiovascular traits. *Diabetologia* **52**, 106–114.
66. Sagoo GS, Tatt I, Salanti G, *et al.* (2008) Seven lipoprotein lipase gene polymorphisms, lipid fractions, and coronary disease: a HuGE association review and meta-analysis. *Am J Epidemiol* **168**, 1233–1246.
67. Tai ES, Adiconis X, Ordovas JM, *et al.* (2003) Polymorphisms at the SRBI locus are associated with lipoprotein levels in subjects with heterozygous familial hypercholesterolemia. *Clin Genet* **63**, 53–58.
68. Acton S, Osgood D, Donoghue M, *et al.* (1999) Association of polymorphisms at the *SR-BI* gene locus with plasma lipid levels and body mass index in a white population. *Arterioscler Thromb Vasc Biol* **19**, 1734–1743.
69. Osgood D, Corella D, Demissie S, *et al.* (2003) Genetic variation at the scavenger receptor class B type I gene locus determines plasma lipoprotein concentrations and particle size and interacts with type 2 diabetes: The Framingham Study. *J Clin Endocrinol Metab* **88**, 2869–2879.
70. McCarthy JJ, Lehner T, Reeves C, *et al.* (2003) Association of genetic variants in the HDL receptor, SR-B1, with abnormal lipids in women with coronary artery disease. *J Med Genet* **40**, 453–458.