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Review Article

Gene-related prevalence of metabolically healthy obesity in different racio-ethnic groups

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ABSTRACT

The metabolically healthy obesity (MHO) phenotype is partly influenced by race/ethnicity and genetic factors being relatively more prevalent in some groups compared to others. This review examines current evidence on the prevalence of MHO amongst children, adolescents and adults of different racio-ethnic groups; and explores gene variants and single nucleotide polymorphisms (SNPs) that may confer cardioprotection in some racio-ethnic groups compared to others. Literature search of articles published in English was conducted using PubMed, Medline and Google scholar databases, with search terms related to the prevalence of metabolically healthy obesity as well as genetic variants that decrease or increase the risk of metabolic syndrome (MetS). MHO prevalence differed across racio-ethnic groups and gene variants that confer cardioprotection were higher in some racio-ethnic groups compared to others. Lower prevalence of MHO across all ages was particularly reported in the Middle East, while high prevalence was reported in Africans, Americans and some Asian adult population. Excluding environmental and other risk factors, we observed that Caucasians were carriers of gene variants that confer protection against cardiometabolic diseases, whilst Asians showed high frequency of gene variants that increase susceptibility to MetS. A robust understanding of the role of these gene variants, their frequency distribution and racio-ethnic variations may facilitate conceptualisation of appropriate genome wide association studies (GWAS) to determine significant associations between various genetic factors and observed phenotype or disease. This will guide policy formulation and serve as a useful tool in pharmacogenomics and precision medicine.

INTRODUCTION

Overweight and obesity are defined as unusual or excessive fat accumulation that may impair health (WHO, 2020). The body mass index (BMI) is commonly used to classify overweight and obesity in adults and it is defined as a person's weight in kilograms divided by the square of their height in metres (kg/m2). World health organisation (WHO) defines overweight as a BMI ≥ 25 kg/m2 and obesity as BMI ≥ 30 kg/m2, while obesity in adults is categorized into class 1 (30-34.9 kg/m2); class 2 (35-39.9 kg/m2) and class 3 (≥ 40 kg/m2) (WHO, 2020). In children under five years of age overweight is weight-for-height greater than two standard deviations (> +2SD) and obesity is weight-for-height greater than three standard deviations (> +3SD). For children aged between 5-19 years, overweight is BMI-for-age greater than one standard deviation (> +1SD) above the WHO growth reference median, and obesity is greater than two standard deviation (> +2SD) above the WHO growth reference median (WHO, 2020). The BMI does not correspond to the same degree of fatness in different individuals. Other measures, such as waist circumference (WC) are better predictors of cardiovascular disease (CVD) risk than BMI. Abdominal overweight is given as (WC 95-102 cm in men; and 81-88 cm in women) and obesity (> 102 cm in men; and > 88 cm in women) (WHO, 2011).]. For adults aged 70 and above, 106 cm in men; and 99 cm in women as cut-offs for abdominal obesity has been suggested by (Heim et al., 2011).

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The global prevalence of obesity has grown to epidemic proportions as it affects about 775 million people worldwide including adults, adolescents and children (Kumar, 2019). Obesity is associated with metabolic diseases including insulin insensitivity, high blood glucose or diabetes, dyslipidaemia and non-metabolic diseases including some cancers (pancreatic, liver, colorectal, post-menopausal breast cancer, kidney and endometrial cancers), osteoarthritis, polycystic ovarian syndrome, non-alcoholic fatty liver disease and pulmonary disease (Dobbins, Decorby and Choi, 2013; Upadhyay et al., 2018). By far, perhaps the most important association of obesity is with CVD, though its contribution to overall mortality from CVD is still debated (Muñoz-Garach et al., 2016). The obese are a heterogenous group in relation to risk of metabolic syndrome (MetS). Risk of CVD is determined by MetS, which comprise a range of abnormalities including high blood pressure (HBP), dyslipidaemia, high fasting plasma glucose (FPG) concentration, inflammation and insulin resistance (IR) (Muñoz-Garach, Cornejo-Pareja and Tinahones, 2016). Interestingly, there is a subset of obese individuals characterised by an apparent decreased susceptibility to MetS. This category of individuals are referred to as the metabolically healthy obese (MHO), a term first described over fifteen years ago (Sims, 2001). Subsequently, a consensus MHO definition has been established in children and adolescents (Table 1) (Damanhoury et al., 2018), but not in adults. Several definitions have been proposed in adults (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Karelis, Brochu and Rabasa-Lhoret, 2004; Meigs et al., 2006; Aguilar-Salinas et al., 2008; Wildman et al., 2008) as shown in Table 2. Metabolic health is influenced by lifestyle, environment, physical fitness, ethnicity, gender and age but these factors are yet to be included in the definition of MHO (Blüher, 2014).

Table 1. Consensus definition of metabolically healthy obesity in children and adolescents (ages 5-19 years).

Cardiometabolic variables	**Values**
HDL-C, mg/dL	> 40
TAG, mg/dL	≤150
BP (SBP and DBP)	≤ 90th percentile
FPG, mg/dL	<100

Adapted from: Damanhoury et al., 2018.

Table 2. Criteria for defining metabolic health status in obese adults

Metabolic components	**Aguilar-Salinas *et al*., (2008)**	**Wildman *et al*., (2008)**	**Karelis *et al*., (2004)**	**NCEP-ATPIII (2001)**	**Meigs *et al*., (2006)**
BP, mmHg	< 140/90 and no treatment	≥ 130/85 or treatment		130/85 or treatment	≥ 130/85 or treatment
WC, cm				≥ 102 (M) ≥ 88 (F)	≥ 102 (M) ≥ 88 (F)
TAG, mg/dL		≥ 150	≤ 150	≥ 150	≥ 150
HDL-C, mg/dL	≥.40	<40 (M) <50 (F)	≥0	< 40 (M) < 50 (F)	<40 (M) <50 (F)
FPG, mg/dL	<126 and no treatment	≥ 100 or treatment		≥ 100 or treatment	≥ 100 or treatment
TC, mg/dL			≤201		
LDL-C, mg/dL			≤ 101		
HOMA-IR		>90th percentile	<1.95		
HsCRP, mg/L		>90th percentile			
MH criteria	All of the above	<2 of the above	≥4 of the above	≤3 of the above	<3 of the above

BMI, body mass index; BP, blood pressure; F, female; FPG, fasting plasma glucose; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein-cholesterol; M, male; MH, metabolically healthy; NCEP: ATPIII, National Cholesterol Education Program-Third Adult Treatment Panel; TAG, triacylglycerol; TC, total cholesterol; WC, waist circumference.

The exact mechanism(s) underlying this heterogeneity in the obese is still not clearly understood. However, studies have reported that both race/ethnicity and genetic predisposition in part, are capable of influencing the MHO phenotype (Forouhi and Sattar, 2006; Berezina *et al.*, 2015). Racio-ethnic differences in the risk of MetS, atherosclerosis, CVD and lipid metabolism have been reported (Forouhi and Sattar, 2006). The observed differences in various racio-ethnic groups may result from differences in inflammatory markers, visceral adiposity, body fat distribution, IR, adiponectin and

plasma homocysteine concentration (Forouhi and Sattar, 2006).

The genetic predisposition of an individual could possibly provide clues and explain the marked differences in the risk of MetS across racio-ethnic groups. Numerous gene variants (mostly single nucleotide polymorphisms, SNPs) are associated with various components of MetS and eventually modify a population's risk to MetS by affecting different critical metabolic pathways (Chang *et al.*, 2018). Whilst the role of gene variants and SNPs associated with the risk of MetS in certain populations have been described (Zadjali *et al.*, 2013; Zhou *et al.*, 2016), data on the frequency distribution of these genetic factors in explaining the prevalence of MHO amongst different racio-ethnic groups are limited. Such data would contribute to our understanding of the biological variations caused by gene variants. This may explain the predisposition of some populations to decreased risk of MetS, which is required to formulate racio-ethnic specific guidelines on primary and secondary prevention of MetS. It could also identify more appropriate screening, diagnostic and treatment strategies in specific populations. Hitherto, whether MHO individuals have some specific gene variants or polymorphisms that confer cardioprotection in different racio-ethnic group is poorly investigated. Therefore, in this review, we examined the prevalence of MHO in different racio-ethnic groups amongst children, adolescents and adults. We also attempted to identify possible gene variants and SNPs that comparatively confer cardioprotection and increase the prevalence of MHO in certain racio-ethnic groups.

Literature search

A literature search was performed from April 2019 to March 2020 on PubMed, MEDLINE and Google Scholar databases, using multiple search terms including obesity; MHO; prevalence of MHO in children, adolescents and adults; prevalence of the MHO phenotype in different ethnicities; racial and ethnic disparities in the prevalence of MetS; and genetic variants in MetS. A search was also conducted for ethnicity and pathogenesis of MHO among children, adolescents and adults; genetic variants that contribute to the risk of MetS in different racio-ethnic group as well as for global frequency distribution of identified genes and the association between SNPs, MetS and MHO. There was no restriction on date of publication and only articles written in English were included.

MHO prevalence in children and adolescents of different racio-ethnic groups

Until 2018, there was no standard MHO definition in children and adolescents (Damanhoury *et al.*, 2018) and only those with obesity fulfilling all of the cardiometabolic criteria shown in table 1 were classified as having MHO (Sims, 2001). However, no agreement has been reached for FPG, even though an FPG of ≤ 100 mg/dL ($\leq$5.6 mmol/L) was the most commonly used criteria in previous studies of MHO in children and adolescents (Damanhoury *et al.*, 2018). Racio-ethnic specific differences have been reported in the prevalence of MHO in children and adolescents. An Italian study of 1201 obese children and adolescents aged 4-18 years, which employed the proposed consensus definition of MHO reported a prevalence of 39% (Genovesi *et al.*, 2020). The estimated prevalence of MHO in children and adolescents differed significantly in previous studies, largely due to variations in definitions employed. Since we could not find a systematic review and meta-analysis on prevalence of MHO in children and adolescents of different racio-ethnic groups, findings of individual studies were reported instead (Table 3).

A cross-sectional study of 340 overweight adolescents in Brazil and Colombia aged 10-18 years reported an MHO prevalence of 49.4% and 55.9% (Remor *et al.*, 2019). A study performed among 1047 obese children and adolescent below 19 years in the Eastern Mediterranean region of the Kingdom of Saudi Arabia found up to 23.8% and 20.9% to be metabolically healthy (Nasreddine *et al.*, 2018). Similarly, another Middle Eastern study in 230 obese Israeli children and adolescent (median age 9.9 years) reported an MHO prevalence of 20.9% (Margolis-Gil *et al.*, 2018). An MHO prevalence of 35.4% has been reported in 659 overweight and obese European adolescents (González-Gil *et al.*, 2018). A retrospective study among 189 obese children and adolescents (ages 4-19 years) of African American/Caribbean descent in the USA reported an MHO prevalence of 38% (Khokhar *et al.*, 2017). Data from the fourth Korea National Health and Nutrition Examination Survey of 530 obese children and adolescents (aged 10-19 years) found an MHO prevalence of 35.4% (Yoon *et al.*, 2017). A large longitudinal study conducted in Germany of 2017 obese children (mean age: 11.6 ± 2.8 years) reported an MHO prevalence of 49.3% (Reinehr *et al.*, 2015). Additionally, a cross-sectional study conducted in Canada reported an MHO prevalence of 21.5-31.5% in 181 overweight obese children and adolescents aged 8-17 years (Prince *et al.*, 2014). Furthermore, an MHO prevalence of 68% was reported from data of 225 obese adolescents (aged 12-18 years) collected from the USA National Health Nutrition Examination Survey of 2003-2004 and 2005-2006 (Camhi *et al.*, 2013).

Overall, the prevalence of MHO was lowest in the Saudi Arabian and Israeli studies, suggesting majority of the

child–adolescent obese population in this region would be metabolically unhealthy (Table 3). This finding is supported by that of (Friend, Craig and Turner, 2013) who reported a higher prevalence of MetS in the Middle East compared to Europe and the Far East. Similarly, a meta-analysis of 59 cross-sectional studies in Middle-East countries reported high prevalence of MetS - Turkey (44%), Saudi-Arabia (16-41%), Qatar (26-33%), Kuwait (9-36%), Emirate (22-50%), Iran (6-42%), and Yemen (23%) (Ansarimoghaddam *et al.*, 2018).

Table 3. MHO prevalence in children and adolescents of different racio-ethnic groups.
BP, blood pressure; CMRF, cardiometabolic risk factor; FBG, fasting blood glucose; HDL-C, high density lipoprotein-cholesterol; IDF, international diabetes federation; IR, insulin resistance; MetS, metabolic syndrome; MHO, metabolically healthy obesity; NR, not reported; TAG, triacylglycerol.

Author, year, country	Ethnic/Racial group	Sample size/BMI category/age group	MHO definition used	MHO prevalence
Genovesi *et al*., 2020, Italy	Caucasians	1201 obese children and adolescents	Based on definition proposed by Damanhoury *et al*. 2018	39%
Remor *et al*., 2019, Brazil and Columbia.	South Americans	340 overweight Children and adolescents	Absence of both MetS components and IR	49.4% & 55.9%respectively
González-Gil *et al*., 2018, Spain	Caucasians	659 overweight and obese adolescents	Based on age and sex cut off for FBG, BP, TAG and HDL-C	35.4%
Margolis *et al*., 2018. Israel	Jews	230 obese children and adolescents	Based on CMRF clustering: BP, serum lipids and glucose	20.9%
Nasreddine *et al.*, 2018, Saudi Arabia.	Arabians	1047 obese children and adolescents	Based on absence of both CMRF and IR according to IDF criteria (Zimmet *et al.*, 2007).	23.8% & 20.9% respectively
Khokhar *et al*., 2017, USA.	African – American/Caribbean	189 obese children and adolescents	NR	38%
Yoon *et al*., 2017, Korea.	Asians	530 obese children and adolescents	Absence of IR and CMRF using IDF criteria (Zimmet *et al.*, 2007)	68.8% and 36.8% respectively.
Reinehr *et al*., 2015, Germany	Caucasians	2017 obese children	Absence of hypertension, dyslipidaemia and impaired fasting glucose	49.3%
Prince *et al*., 2014, Canada	Caucasians	181 obese children and adolescents	Obesity with no CMRF and obesity with HOMA-IR of ≥ 3.16	31.5% & 21.5% respectively
Camhi *et al*., 2013, USA.	Non–Hispanic white and blacks, Hispanic and others.	225 obese adolescents	Absence or one CMRF: (TAG, HDL-C, BP or FBG)	68%

MHO prevalence in adults of different racio-ethnic groups

Due to lack of a standard MHO definition and disparity of employed criteria, establishing an accurate or standard prevalence of MHO in adults in different studies and racio-ethnic groups has been challenging (Liu *et al.*, 2019). A meta-analysis of 40 population-based investigations and intervention studies performed in Europe, Southeast Asia, Middle East, Africa, North and South America and Australia, observed an overall MHO prevalence of 35% in obese adults (Lin *et al.*, 2017). Some regions were reported to have a higher prevalence as observed in Africans followed by South Americans (Table 4). However, in this meta-analysis, only one study each was conducted in both Africans and South Americans. There was a similarity between MHO prevalence in Southeast Asia, North America and

Australia, and the lowest MHO prevalence was recorded in Europe and the Middle East (Lin *et al.*, 2017). Included studies defined metabolic health based on age and gender-specific cut-offs of metabolic components defined by the Third Report of National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) or International Diabetes Federation (IDF) i.e. systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein -cholesterol (HDL-C), triacylglycerol (TAG), and FPG (NCEP-ATP III 2001).

As reported in children and adolescents, a lower MHO prevalence has also been found in adults from the Middle East. The distinct patterns of fat distribution by ethnicity may influence the variation observed amongst different ethnic groups as Blacks are shown to have less visceral abdominal fat accumulation compared to their White counterparts (Rahman *et al.*, 2009; Heymsfield *et al.*, 2016). The higher MHO prevalence in Africans is also supported by lower prevalence of MetS in Blacks (Krishnadath *et al.*, 2016). Low prevalence of MetS in Blacks occurs despite higher rates of IR, inflammation, and HBP (Deboer, 2011), but lower tendency for dyslipidaemia, central obesity and increased FPG concentration (Walker *et al.*, 2012).

Additionally, a worldwide meta-analysis of 32 population based cross-sectional and longitudinal studies consisting of obese Europeans, Asians and Americans reported an MHO prevalence of 28.5% (Wang *et al.*, 2015). The American population had the highest MHO prevalence and included studies employed seven definitions of metabolic health including definitions by Meigs (Meigs *et al.*, 2006), Wildman (Wildman *et al.*, 2008), Aguilar-Salinas (Aguilar-Salinas *et al.*, 2008), Guerrero (Guerrero-Romero and Rodriguez-Moran, 2013), Calori (Calori *et al.*, 2011), Soriguer (Soriguer *et al.*, 2013) and Hamer (Hamer, Batty and Kivimaki, 2012). Furthermore, a systematic review of 27 population-based studies conducted in Asia, Europe, North America and Oceania reported a MHO prevalence of 6-75% (Rey-López *et al.*, 2014). The included studies employed 30 different definitions of metabolic health, with the definition by Karelis *et al.* 2004 that included five cardiometabolic factors i.e. triglycerides, HDL-C, LDL-C, total cholesterol and HOMA-IR with stricter diagnostic criteria (4 out of 5) (Karelis *et al.*, 2004) being the most commonly used. However, majority (96%) of included studies did not report the 95% confidence interval for MHO prevalence. Some ethnic groups had healthier metabolic profile compared to others and MHO prevalence was higher in Asians compared to Caucasians or people of multi-ethnic origin (Rey-López *et al.*, 2014). This observation is contradictory, since Asians are particularly more prone to abdominal obesity and visceral fat accumulation and are at a higher risk of type 2 diabetes mellitus (T2DM) and CVD compared to Europeans (Misra and Vikram, 2004; Misra and Khurana, 2009). Amongst the prevalence rates stated for the aforementioned meta-analysis, only (Lin *et al.*, 2017) included a study in Africans. Thus, there is limited data on the prevalence of MHO in Africans, as they have seldom been included in existing studies.

Possible genetic basis for the racio-ethnic disparities in MHO.

As earlier stated, MHO prevalence show racio-ethnic disparities. It was observed to be particularly low in children and adolescents from Middle East. Adult rates are higher in Africans and South Americans, but lower in Europeans and Middle easterners (Table 4). It is important to note that the possible genetic mechanisms that could contribute to a high prevalence of MHO could be inherited at birth and persist through adulthood.

Table 4. Prevalence of metabolically healthy obesity in adults of different race/ethnicity

Region	Metabolically healthy obesity prevalence, proportion (95% CI)
Africa	0.86 (0.81-0.91)
South America	0.71 (0.65-0.76)
North America	0.43 (0.32-0.53)
Australia	0.38 (0.34-0.41)
South East Asia	0.37 (0.28-0.46)
Europe	0.26 (0.19-0.34)

Adapted from (Lin et al., 2017).

It is believed that certain gene variants and SNPs exist that confer protection against cardiometabolic diseases or decrease the risk of MetS (Schlauch *et al.*, 2019). Some racio-ethnic groups may have a higher frequency of these cardioprotective gene variants. The study by (Schlauch *et al.*, 2019) appears to be the first and perhaps the only study to genetically screen 38 metabolically healthy American class 2 and 3 obese women of European descent for SNPs that confer protection to the development of cardiometabolic disease. This study found SNPs in *KCNQ1* and *TOX2* to likely confer this protection. Thus, there is need to identify candidate gene variants and SNPs that may confer protection to the development of MetS or specifically related to MHO. In this review, we identified and discussed nine genes and their gene variants or SNPs that may possibly affect MetS risk and are associated with the MHO phenotype. These include: TOX high mobility group box family member 2 (*TOX2*), Potassium voltage-gated channel

subfamily Q member 1 (*KCNQ1*), methylenetetrahydrofolate reductase (*MTHFR*), adiponectin (*ADIPOQ*), dual specificity protein phosphatase 10 (*DUSP10*), leptin (*LEP*) and leptin receptor (*LEPR*), bromodomain containing protein 2 (*BRD2*), cholesteryl esteryl ester-transfer protein (*CETP*) and Apolipoprotein A5 (*APOA5*) genes (Fig. 1).

TOX high mobility group box family member 2 (TOX2) gene

Decreased expression of *TOX2* gene may decrease MetS risk, as three SNPs (rs766622, rs6065690 and rs6093921) in an intronic region of *TOX2* gene have been reported to be associated with the MHO phenotype in 38 metabolically healthy class 2 and 3 obese American women of European descent (Schlauch *et al.*, 2019). *TOX2* is located on chromosome 20q13 and indirectly regulates TBX21 (T-bet, a T-box transcription factor family member that regulates immune cell differentiation and function) by decreasing its expression (Stolarczyk, Lord and Howard, 2014; Vong *et al.*, 2014). TBX21 is the primary transcription factor for T-helper 1 (Th1) cell development and plays a critical role in activation of innate immune cells such as dendritic, lymphoid, natural killer (NK) and T-cells (Garrett *et al.*, 2007). TBX21 regulates the balance between Th1 and Th2 responses in inflammatory diseases (Buono *et al.*, 2005), and transactivates the interferon-γ (IFN-γ) gene (Szabo *et al.*, 2002). An imbalance of Th1/Th2 cells has been observed with increasing adiposity as adipose tissue contain immune cells in the stromalvascular fraction (Ferrante, 2013; Stolarczyk, Lord and Howard, 2014).

Decreased *TBX21* gene expression may be associated with MHO, as T- bet deficient (T-bet$^{-/-}$) mice with increased visceral fat display altered adipose tissue immune cell infiltration, reduced proinflammatory cytokines, lower fasting insulin concentration, and better glucose tolerance, hence were more insulin sensitive compared to wild type (WT) mice (Stolarczyk *et al.*, 2013). This suggest that polymorphisms that lead to decreased *TOX2* expression may indirectly affect obesity through a TBX21-dependent mechanism.

Potential mechanisms through which TBX21 (T-bet) may improve insulin sensitivity are as follows: First, through reduced secretion of IFN-γ, which has been reported to improve glucose homeostasis and cytokine expression in diet-induced obesity (O'Rourke *et al.*, 2012), suggesting a role for IFN-γ in regulating inflammation and glucose homeostasis in obesity. Second, through its interaction with forkhead box P3 (Foxp3^{+}) T cells (Tregs), as the anti-inflammatory action of Tregs alters insulin sensitivity (Feuerer *et al.*, 2009). Due to limited data on the association between *TOX2* gene and metabolic health in humans, we could not assess the prevalence of MHO in different racial or ethnic groups in relation to TBX21. Hence, there is need for more genetic studies to evaluate the role of *TOX2* gene in MHO.

Potassium voltage–gated channel subfamily q member 1 (KCNQ1) gene

A SNP in *KCNQ1* has been reported to be associated with MHO phenotype (Schlauch *et al.*, 2019). *KCNQ1* is located on chromosome 11q15 and encodes a protein that is essential for the repolarization phase of cardiac action potential (Al-Shammari *et al.*, 2017; Liu *et al.*, 2018). Hence, polymorphisms in *KCNQ1* may impair heart function, resulting in increased risk of CVD (Fosmo and Skraastad, 2017). It has been implicated in various cardiac dysfunctions caused by abnormal lipid metabolism (Chen *et al.*, 2010), familial atrial fibrillation (Bartos *et al.*, 2013) and long QT syndrome (Hajjar and Hulot, 2014). Gene variants in *KCNQ1* may also be involved in the metabolism and balance of blood glucose, following its significant association with impaired FBG or haemoglobin A1c (HbA1c) (Qi *et al.*, 2009). Polymorphisms in *KCNQ1* may also be responsible for impaired pancreatic β-cell function (Rosengren *et al.*, 2012) and reduced insulin secretion following an oral glucose load overtime (Holmkvist *et al.*, 2009), and thus predispose to T2DM (Yasuda *et al.*, 2008; Scott *et al.*, 2017).

Several variants of *KCNQ1* (>600 disease associated variants) have been found but variants rs2237892, rs227897 and rs2237897 have the strongest association with MHO. Of these, *KCNQ1* rs2237892 is the most widely studied and is significantly associated with increased T2DM risk in Europeans, Americans and Asian population (W. Zhang *et al.*, 2015). Of the various *KCNQ1* rs2237892 alleles (CC, CT and TT), the CC allele has been reported to increase the susceptibility to T2DM by influencing β cell function and insulin secretion (Li, Wang and Lu, 2014), as well as increased hypertension and macrovascular complications in Chinese Han patients with T2DM compared to alleles TT and CT (W. Zhang *et al.*, 2015). This may suggest that increased MetS risk is found in individuals or racio-ethnic groups with a high frequency distribution of the C allele of rs2237892 variant, while reduced risk of MetS would be associated with T allele of rs2237892. A lack of association of *KCNQ1* rs2237892 with T2DM has also been reported in Saudi population and North African Arabs (Turki *et al.*, 2012; Al-Shammari *et al.*, 2017). However, studies of *KCNQ1* rs2237892 C-T polymorphism among people of African descent and the Middle East is currently limited. Other studies have shown people of Asian descent to have a higher

frequency of *KCNQ1* rs2237892 CC allele (Li, Wang and Lu, 2014).

Methylenetetrahydrofolate reductase (MTHFR) gene

Polymorphisms in *MTHFR* have been reported to increase risk of MetS, thereby worsening metabolic health (LI *et al.*, 2011). A meta-analysis of 30 case-control studies found *MTHFR* C677T (rs1801133) polymorphism to be associated with risk of myocardial infarction (MI) in young and middle-aged Caucasians (Xuan *et al.*, 2011). *MTHFR* gene located on chromosome 1p36.3 (Wan *et al.*, 2018) modulates homocysteine (Hcy) metabolism, due to its ability to maintain normal serum/plasma Hcy concentration (Trimmer, 2013). Increased circulating Hcy concentration may increase the risk of MetS by producing oxygen-free radicals which stimulates the proliferation of vascular smooth muscle cells, inducing IR and damaging vascular endothelial cell function. This results in increased plasma C-reactive protein levels, promotion of lipid peroxidation, and a decrease in APO-A1 expression, thereby affecting other pathophysiological processes (Hajer *et al.*, 2007). Hcy may induce apoptosis of endothelial progenitor cells via enhancement of endoplasmic reticulum stress-mediated activation of caspase-3. Hcy exposure can weaken the viability of insulin-secreting cells, reduce glucokinase phosphorylating ability, and decrease insulin secretory responsiveness leading to cell death (Huang *et al.*, 2013).

Several SNPs in *MTHFR* have been described but C677T (rs1801133) is the most studied and clinically relevant (El Shafie *et al.*, 2017). This SNP is the most common genetic cause of Hyper-homocysteinemia (HHcy), which has been implicated in the pathogenesis of atherosclerosis (LI *et al.*, 2011) . This polymorphism causes the enzyme to become thermolabile with 50-70% reduced MTHFR enzyme activity and HHcy particularly in the presence of low dietary folate (Munisamy *et al.*, 2015). Among the various allele types of *MTHFR* C677T (CC, CT and TT), individuals who are homozygous for TT allele have an increased risk of HHcy (Wang *et al.*, 2018), hypertension (Ward *et al.*, 2011), T2DM (B. Zhu *et al.*, 2014) and dyslipidaemia (Real *et al.*, 2009). This has been confirmed in a Chinese population where the TT allele carriers had 1.6 times higher risk of developing MetS than did CC allele carriers (Wang *et al.*, 2018). This finding may suggest that MHO individuals would have less occurrence of the TT allele and a higher incidence of the CC indicating that the CC and CT allele may confer protection against MetS. However, this hypothesis has not been investigated in MHO individuals.

The frequency of *MTHFR* C677T particularly the homozygous T allele varies in different geographical regions and ethnic groups (Botto and Yang, 2000). A north-to-south increase in allele frequency was observed in Europe (Botto and Yang, 2000) with the allele frequency reported to be 0.07 in sub-Saharan Africans and 0.06 in Canadian Inuit, whilst in whites, Japanese, and Chinese, the allele frequencies ranged from 0.24–0.54 (Hegele *et al.*, 1997; Pepe *et al.*, 1998). More recently, a meta-analysis of 62 studies reported the lowest frequency of *MTHFR* C677 TT allele in Africans (10.3 %), and highest in Europeans (34.1 %) (Yadav *et al.*, 2017). This could possibly contribute to the higher prevalence of MHO in Africans. Although these studies have not included frequencies in Arabians, evidence from global maps revealed that the highest polymorphism on *MTHFR* C677 TT allele were found in the Middle East (Iran and Saudi Arabia), Europe (Cyprus, Spain, Germany, Slovenia, and United Kingdom), Asia (Japan and China), and North America (Canada and United States) for the general healthy population (Gonzales, Yu and Shiao, 2017). This finding could also support the increase in MetS and decrease in MHO reported in children, adolescents and adults in Middle East.

Adiponectin (ADIPOQ) gene

Increased adiponectin concentrations have been observed in MHO women compared to their metabolically unhealthy counterparts, suggesting that high adiponectin concentrations may determine the favourable metabolic profile of the MHO (Tailor *et al.*, 2010). This indicates that gene variants and polymorphism in *ADIPOQ* that increase adiponectin concentration are crucial to improving metabolic health. Adiponectin gene, also known as *ACRP30, ADIPOQ* and *GBP28* (Pajvani and Scherer, 2003), is located on chromosome 3q27 and regulates glucose concentration, fatty acid oxidation, cardiovascular function and improves IR, since it has anti-diabetic, anti-inflammatory and anti-atherogenic properties (Ruan and Dong, 2016).

Potential mechanisms by which adiponectin exerts its anti-atherogenic properties include: inhibition of the expression of adhesion molecules in endothelial cells, smooth muscle cell proliferation, differentiation of monocytes into macrophages, formation of foam cells and secretion of TNF-α by macrophages (Arita *et al.*, 2002; Lenz and Diamond, 2008). Adiponectin increases endothelial nitric oxide secretion (Chandran *et al.*, 2003), and exerts an anti-inflammatory effect through the activation of its three receptors - AdipoR1, AdipoR2, and T-cadherin (Robinson, Prins and Venkatesh, 2011).

The activation of AdipoR1 and R2 results in increased hepatic and skeletal muscle fatty acid oxidation, increased skeletal muscle lactate production, reduced hepatic gluconeogenesis, increased cellular glucose uptake, and inhibition of inflammation and oxidative stress (Robinson, Prins and Venkatesh, 2011).

Several SNPs in *ADIPOQ* gene influence adiponectin concentration and are associated with risk of MetS (Jang *et al.*, 2008). The most widely studied of these SNPs are *ADIPOQ* rs2241766 (+45 T > G in exon2) and rs1501299 (+276 G > T in intron2) (Melistas *et al.*, 2009). *ADIPOQ* rs1501299 SNP may decrease CVD risk (Yuan *et al.*, 2016; Kanu *et al.*, 2018; Song, Yoon and Kim, 2018), as homozygote TT for SNP rs1501299 had a lower CVD risk than carriers of other genotypes (Menzaghi, Trischitta and Doria, 2007), and are protected from MI (Chiodini *et al.*, 2010). Their protective role may be due to their ability to increase serum adiponectin concentration (Song, Yoon and Kim, 2018; Christodoulou *et al.*, 2020), suggesting that populations with this SNP would have a higher prevalence of MHO compared to those with a lower frequency. Unfortunately, there is limited data on the frequency distribution of SNP *ADIPOQ* rs1501299 T allele in different racio-ethnic groups, hence, conclusion on whether Africans or Asians are carriers of this protective gene variant could not be made**.** This may be attributed to lack genome wide association studies (GWAS) of the gene variant in different racio-ethnic groups.

Given the reported high prevalence of MHO in Africans, Americans and some Asians, it would be expected that these ethnic groups would have higher adiponectin concentration. However, lower concentration of adiponectin have been reported in Blacks (10.4µg/mL) compared to Whites (14.9µg/mL) (Cohen *et al.*, 2011). Additionally, adiponectin concentration are significantly higher in Canadians of European descent (12.96 ± 0.73 µg/mL) and Aboriginal people (11.87 ± 0.41 µg/mL) than in South Asians (9.35 ± 0.43 µg/mL) and Chinese (8.52 ± 0.57 µg/mL) (overall $P < 0.001$) (Mente *et al.*, 2010).

Dual specificity protein phosphatase 10 (DUSP10) gene

Increased *DUSP10* expression decreases the risk of MetS and may be associated with the MHO phenotype due to its potent anti-inflammatory properties (Arkan *et al.*, 2005). *DUSP10* also known as MAP kinase phosphatase 5 (*MKP5*) gene is located on chromosome 1q41 and negatively regulates p38 MAPK and c-Jun N-terminal kinase (JNK) through their dephosphorylation (Caunt and Keyse, 2013). *DUSP10* is highly expressed in insulin responsive tissues including skeletal muscle, adipose tissue and liver of humans and mice, thus, it regulates obesity, inflammation, IR, insulin sensitivity suggesting a potential role in metabolic regulation (Y. Zhang *et al.*, 2015). Increased *DUSP10* promotes the dephosphorylation of JNK1 pathway resulting in improved metabolic health. Although this hypothesis has not been investigated in MHO individuals, overexpression of *DUSP10* inhibits the development of inflammation in the liver preventing the onset of age-associated and diet-induced non-alcoholic fatty liver disease (NAFLD) by inhibiting p38 activation. This results in decreased peroxisome proliferator-activated receptors (PPARγ) expression which in turn decreases hepatic lipid accumulation, inflammation, and fibrosis (Tang *et al.*, 2019). Similarly, overexpression of *DUSP10* in prostatic epithelial cells acts as an anti-inflammatory protein, decreasing pro-inflammatory responses mediated by cytokine-dependent NF-kB activation, COX-2 expression, and cytokine (IL-6 and IL-8) (Nonn, Duong and Peehl, 2007).

However, decreased *DUSP10* expression promotes a phosphorylated JNK activation which has been reported to increase risk of MetS (Hirosumi *et al.*, 2002). *DUSP10* deficient mice have shown increased adiposity, developed glucose intolerance, impaired insulin sensitivity and increased expression of proinflammatory cytokines, including IL-1β, IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) compared to age-matched WT mice *(*Zhang *et al*., 2015).

Although the role of *DUSP10* gene in MHO humans has not been fully established, it is possible that enhanced expression of *DUSP10* may exert some protection against MetS. However, it is not known if there is a differential expression of *DUSP10* in people of Asian, African, Arabian and Caucasian descent. Although several *DUSP10* SNPs including rs1118838, rs12724393, rs908858 and rs6687758 have been implicated in the risk of colorectal cancer (Zhang *et al.*, 2014), association with metabolic disease is yet to be determined.

Leptin (LEP) & leptin receptor (LEPR) gene

Though plasma leptin levels are higher in obesity, lower leptin concentration has been associated with MHO compared to their metabolically unhealthy counterparts (Tailor *et al.*, 2010). Leptin and its receptor located on chromosome 1p31 function in regulating energy homeostasis (Schwartz *et al.*, 2000). The physiological function of leptin is mediated by its receptor, which is a cytokine receptor that promotes gene transcription by activating signal transduction (Banks *et al.*, 2000). They have been implicated in the pathophysiology of obesity, T2DM and cardiovascular homeostasis (Brennan and Mantzoros, 2006). *LEP* and *LEPR* variants may affect vascular tone in heart

or peripheral circulation, predisposing patients to hypertension and coronary artery disease (CAD) (Nowzari *et al.*, 2018) due to their role in regulating lipid metabolism, blood pressure and angiogenesis (Boumaiza *et al.*, 2012).

Several SNPs have been identified in the coding and non-coding regions of the *LEPR* gene (Daghestani *et al.*, 2019). Of these SNPs, *LEPR* polymorphism Q223R (rs1137101) also known as Gln233Arg is the most frequently studied and is associated with impaired *LEPR* signalling capacity, with higher mean circulating concentrations of leptin (Ragin *et al.*, 2009) and increased risk of MetS as it has been linked to dyslipidaemia (Okada *et al.*, 2010), T2DM (Yang *et al.*, 2016) and atherosclerosis (Saukko, Kesäniemi and Ukkola, 2010). Populations exhibiting this polymorphism would less likely be metabolically healthy and may have higher leptin concentration.

LEPR Q223R has three genotypes, AA, AG and GG with the GG allele increasing risk of lipid abnormalities and IR particularly in the obese. AA and AG genotypes modify the risk of hyperlipidaemia in obese Saudi women (Daghestani *et al.*, 2019). Obese females with the AA genotype had the lowest leptin and insulin concentration compared to those with the GG genotype who also had higher homeostatic model assessment of insulin resistance (HOMA-IR) (Daghestani *et al.*, 2019). The wild type A allele is highest in Saudis (0.798), British (0.610), Puerto Ricans (0.610), Colombians (0.520), Punjabi Pakistan (0.573), Lubya in Kenya (0.596), Tuscani in Italy (0.561), Europeans (0.531), Americans (0.563), East Asians including Chinese (0.131) and Japanese (0.154) (Daghestani *et al.*, 2019).

It is unexpected for Saudis to have a high frequency of the A` allele since Middle Eastern people were reported to have a low MHO prevalence across all age groups. However, the higher frequency of A `allele reported in this study was not associated with higher glucose concentration or IR (Daghestani *et al.*, 2019). In addition, among the various ethnic groups represented, Asians have the lowest frequency of the A` allele suggesting increased MetS risk. According to (Bender *et al.*, 2011) Q223R allele frequency is higher in Asians (80.6-95.0%) compared to 30.2-56.7% in Caucasians.

Serum leptin concentration show ethnic variation, as they are significantly higher in South Asians (11.82 ± 0.94 ng/mL) and Aboriginal people (11.13 ± 1.21 ng/mL) than in Europeans (9.12 ± 0.85 ng/mL) and Chinese (8.25 ± 0.77 ng/mL) (overall $P < 0.001$) (Mente *et al.*, 2010).

Bromodomain containing protein 2 (BRD2) gene

Animal models have shown decreased cardiometabolic risk following reduced expression of *BRD2* gene (Wang, Deeney and Denis, 2013), suggesting that reduced expression of this gene could be associated with the MHO phenotype. The *BRD2* is located on chromosome 6p21 and is highly expressed in pancreatic β-cells, where it inhibits β-cell mitosis and insulin transcription (WANG *et al.*, 2009). The *BRD2* gene belongs to the bromodomains and extra terminal domain (BET) family of transcriptional co-regulators that modulates body energy balance and immune function (Taniguchi, 2016). There is evidence that genetically engineered mice deficient in *Brd2* gene did not show inflammation and obesity-induced IR but exhibited improved glucose tolerance, increased adiponectin concentration, reduced macrophage infiltration in white adipose tissue and decreased blood glucose, resulting in improved metabolic profile devoid of T2DM gene (Wang, Deeney and Denis, 2013). MHO individuals show reduced levels of inflammation compared to other obese individuals, protecting them against IR and metabolic dysfunction (Belkina and Denis, 2010). Therefore, it is plausible that the MHO would have reduced expression of *BRD2* gene. Whether the MHO have diminished expression of *BRD2* gene is yet to be established in humans. However, several SNPs have been observed in *BRD2* gene including rs9276935, rs55912052 and rs516535 (Yavuz *et al.*, 2012), but hitherto, none of these have been linked with metabolic health.

Cholesteryl ester transfer protein (CETP) gene

Polymorphisms in the *CETP* gene which results in decreased CETP expression are associated with improved CVD risk profile (Mabuchi, Nohara and Inazu, 2014), indicating an association with MHO phenotype. Decreased plasma CETP activity has been reported to be anti-atherogenic as it increases plasma high density lipoprotein –cholesterol (HDL-C) concentration (Mabuchi, Nohara and Inazu, 2014). The human *CETP* gene is located on chromosome 16q21 and modulates lipid metabolism, particularly HDL-C (Wang *et al.*, 2013). Evidence in CAD patients show that CETP inhibitors increase HDL-C concentration (Lüscher, von Eckardstein and Simic, 2012).

The *CETP* gene is highly polymorphic (Ridker *et al.*, 2009), with over 180 SNPs, but *CETP* Taq1B site rs708272 is the most widely studied (Thompson *et al.*, 2008). Of the various *CETP* Taq1B alleles (B1B1, B1B2 and B2B2), carriers of Taq1B B2B2 genotypes had significant higher HDL-C concentration and lower mean CETP activity compared to carriers of Taq1B B1B1 allele (Thompson *et al.*, 2008). The Taq1B B2B2 tends to decreases the risk of MetS, hence, individuals with this variant may be metabolically healthier. A case control study found the absence of B2 allele to be

associated with a two-fold increased risk of CAD (Tayebi *et al.*, 2013). This study discovered that Taq1B B2B2 genotypes conferred a significant reduced risk of coronary atherosclerosis due to its ability to raise plasma HDL-C concentration (Kashani Farid *et al.*, 2010). Though the exact mechanism of the link between *CETP* SNPs to metabolic health is not clear, it could be via its association with plasma HDL-C concentration. HDL-C is protective of CAD and an inverse association has been recorded (Hausenloy and Yellon, 2008). HDL-C prevents the oxidation of LDL-C on endothelial cell and also induces endothelial cell to produce nitric oxide (Yuhanna *et al.*, 2001).

CETP Taq1B polymorphism varies in different ethnic group, the B2B2 allele frequency - Tunisians (0.29) (Rejeb *et al.*, 2008), African Americans (0.26) (Cuchel *et al.*, 2002), Europeans (0.43) (Gudnason *et al.*, 1999), Americans (0.44) (Ordovas *et al.*, 2000), Israelis (0.43) (Kark *et al.*, 2000) and Taiwanese (0.42) (Hsu *et al.*, 2002). Interestingly, people of African descent had the lowest frequency of this cardioprotective gene variant, despite having a lower tendency of dyslipidaemia. Similarly, a study which compared the frequency of *CETP* Taq1 B2 allele between African Americans and Caucasians found lower frequencies in healthy African Americans (0.26) than in Caucasians (0.44); and patients undergoing cardiac catherization - African Americans (0.28) and Caucasians (0.38) (Cuchel *et al.*, 2002). It is important to note that Africans are under-represented in most genetic studies and instead African Americans who are African with an admixture of Europeans have been used as the sole representative of African population. Much of what is currently reported about genetic diversity comes from Caucasian and Asian population.

Apolipoprotein A5 (APOA5) gene

In human and animal models, *APOA5* gene expression is inversely associated with circulating plasma Triacylglycerol (TAG) concentration. Mice deficient in *Apoa5* gene showed four times greater plasma TAG concentration, whereas the overexpression of *APOA5* gene led to 66% decrease in plasma TAG concentration (Merkel *et al.*, 2005). Obese individuals exhibit lower APOA5 concentration suggesting an increased risk of CVD (Su, Kong and Peng, 2018). Apolipoprotein A5 gene is located on chromosome 11q23 and regulates lipid metabolism, particularly plasma TAGs and HDL-C concentration (Li and Guo, 2014). Potential mechanisms through which *APOA5* may contribute to increased risk of MetS include: decreasing HDL-C concentration (Cha *et al.*, 2014) and modulating hepatic TAG metabolism and its secretion within hepatocytes (Olofsson, 2005). APOA5 attenuates the second step of very low-density lipoprotein (VLDL) particle maturation, vital for the formation of TAG rich VLDL, thereby impairing liver VLDL assemblage and secretion in hepatocytes (Walther and Farese, 2012). APOA5 was found to cause an increase in lipolysis by increasing lipoprotein lipase (LPL) activity and increased removal of TAG rich lipoproteins (Grosskopf *et al.*, 2005).

Of all the variants of *APOA5* gene, rs662799 (-1131T>C) is the most widely studied (W. Zhu *et al.*, 2014). *APOA5* rs662799 contributes to a pro-atherogenic lipoprotein profile, since it is associated with high TAG and reduced HDL-C concentration (Jiang *et al.*, 2010). In 201 MetS patients, the -1131T allele gene variant of *APOA5* significantly increased MetS risk compared to 210 healthy controls indicating this variant is a risk factor for increased TAG and development of MetS (Maász *et al.*, 2007). This suggests that MHO individuals may have decreased prevalence of this variant but this hypothesis has not been investigated.

The allele frequency of *APOA5* rs662799 show inter-ethnic variations. The minor allele of *APOA5* rs662799 has a greater frequency in Japanese and Chinese population compared to Caucasians (Aouizerat *et al.*, 2003). The CC and GG allele in *APOA5* rs662799 show 36.1% higher plasma TAG concentration and increases risk of MetS compared to the TT genotype (Jiang *et al.*, 2010). According to the HapMap database, there are ethnic differences in *APOA5* rs662799 G allele (A>G). The minor allele frequency in European populations (HapMap-CEU) is 1.7%, much lower than the 13.3% observed in individuals of African descent (HapMap-YRI), 26.7% in Chinese (HapMap-CHB) and 28.9% in Japanese (HapMap-JPT) (Ye *et al.*, 2015). A cross sectional study in North Iranian population reported a frequency of 5% close to that of Europeans (Halalkhor *et al.*, 2014). The C allele frequency of *APOA5* rs662799 varies - Hungarian (8.5%) (Maász *et al.*, 2007), Japanese (35.3%) (Yamada *et al.*, 2007), Hong Kong (28.6%) (Ong *et al.*, 2011), Chinese (21.6%) (Xu *et al.*, 2013), Germany (7%) (Grallert *et al.*, 2007), and Taiwanese (27.2%) (Lin *et al.*, 2016). The frequency distribution of both G and C allele have shown higher and lower frequencies in Asians and Europeans respectively. This supports the high visceral fat accumulation and higher risk of T2DM and CVD observed in Asians compared to Europeans.

We are aware that a vast majority of present-day humans across all continents, and in different racial/ethnic groups have notable mixed ancestry or ancestral heterogeneity, which supports admixture. For example, uniformly categorizing admixed African Americans (with ancestries from both Africa and Europe) with the

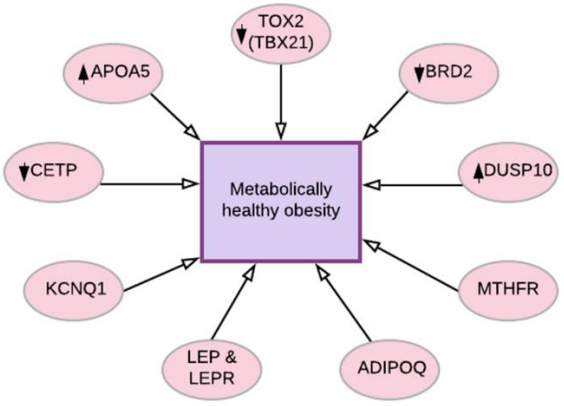

Figure 1. Genes possibly associated with metabolically healthy obesity phenotype. *ADIPOQ*, Adiponectin; *APOA5*, Apolipoprotein A5; *BRD2*, Bromodomain containing protein 2; *CETP*, Cholesteryl ester transfer protein; *DUSP10*, Dual specificity protein phosphatase 10; *KCNQ1*, Potassium voltage–gated channel subfamily q member 1; *LEP* & *LEPR*, Leptin and leptin receptor gene; *MTHFR*, Methylenetetrahydrofolate reductase; *TOX2*, TOX high mobility group box family member 2; *TBX21*, T-box transcription factor 21 ⬆Increased Expression, ⬇Decreased Expression.

racial label Black may not capture inter-continental admixture (Baker *et al.*, 2017). We also acknowledge that ancestral diversity may influence a population's cardiometabolic disease (CMD) risk suggesting that some of the susceptibility to CMD-related traits or diseases may be influenced by genetic factors, which may be ancestry-specific (Fernández-Rhodes *et al.*, 2020). Thus, given differences in allele frequencies across populations, estimating and accounting for ancestral diversity is necessary for appropriately determining the influence of genetic factors on CMD (Fernández-Rhodes *et al.*, 2020). However, as this is beyond the scope of this review, further investigations assessing the impact of ancestral diversity on CMD risk in specific populations are necessary.

FURTHER RESEARCH

Based on the limitations identified in this review, we recommend the following for further research:

- Prevalence of MHO in Africans living in Africa.
- Genetic studies to evaluate the role of TBOX in MHO individuals of different ethnic groups.
- The differential expression of DUSP10 in people of Asian, African, Arabian and Caucasian descent.
- KCNQ1 rs2237892 C-T polymorphism among Africans and indigenes of the Middle East. Previous genetic studies included African Americans/Caribbean as the sole representative of Africans. Much of the available data are those obtained from Caucasians and Asians.
- GWAS of ADIPOQ rs1501299 T allele in different racio-ethnic groups.
- Deficiency of BRD2 gene in MHO humans.

CONCLUSION

As highlighted in this review, the available data/evidence show that MHO prevalence differs amongst racio-ethnic groups. This also supports existing data on prevalence of MetS in different racio-ethnic groups. Lower prevalence of MHO across all ages was particularly reported in the Middle East, while high prevalence was reported in African, American and some Asian adult population. Excluding environmental and other risk factors, we observed that genetic predisposition influences the MHO phenotype across different racio-ethnic groups. Africans had the lowest frequency of *MTHFR* C677T T allele that increases MetS risk compared to their European and Asian counterparts. Despite high MHO prevalence in Africans in the reported/included studies, they had the lowest frequency of the cardioprotective gene variant *CETP* Taq1B B2 allele. On the other hand, Europeans who had highest frequency of *MTHFR* C677T T allele, also showed favourable frequencies of cardioprotective gene variants and SNPs including increased *LEPR* Q223R A and *CETP* Taq1B B2 alleles; and low *APOA5* rs662799 C and G alleles. Furthermore, the low MHO prevalence across all age groups in the Middle East was supported by highest frequency of *MTHFR* C677T T. However, they also had the highest frequency of the cardioprotective *LEPR* Q223R A allele. Overall, Asians had higher frequencies of gene variants and SNPs (*APOA5* rs662799 C and G allele, *LEPR* Q223R A´ allele, *MTHFR* C677T T allele and *KCNQ1* rs2237892) that increase the risk of MetS, thereby decreasing metabolic health.

Gene variants and SNPs for *TOX2*, *DUSP10* and *BRD2* that improve MHO phenotype across different ethnicities are still unknown. Investigating potential gene variants/SNPs for these genes among both metabolically healthy and unhealthy populations in different racio-ethnic groups is necessary. A more robust understanding of the role of these gene variants/SNPs, their frequency distribution and racio-ethnic variations may facilitate conceptualisation of appropriate GWAS to determine significant associations between various genetic factors and observed phenotype or disease. This will guide policy formulation and serve as a useful tool in pharmacogenomics and precision medicine.

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CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

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The review idea was conceptualized by EA, FOR and TA. TA assisted by EA performed the literature search. TA, EA, FOR and ESFO drafted the manuscript with TA and FOR leading the process. All authors reviewed and approved the final draft before submission for publication.

REFERENCES

Aguilar-Salinas CA, García EG, Robles L, Riaño D, Ruiz-Gomez DG, García-Ulloa AC, et al. (2008). High adiponectin concentrations are associated with the metabolically healthy obese phenotype. *J Clin Endocrinol Metab*. 93(10):4075–9.

Al-Shammari MS, Al-Ali R, Al-Balawi N, Al-Enazi MS, Al-Muraikhi AA, Busaleh FN, et al. (2017). Type 2 diabetes associated variants of KCNQ1 strongly confer the risk of cardiovascular disease among the Saudi Arabian population. *Genet Mol Biol*. 40(3):586–90.

Ansarimoghaddam A, Adineh HA, Zareban I, Iranpour S, HosseinZadeh A, Kh F (2018). Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. *Diabetes Metab Syndr*. 12 (2):195–201.

Aouizerat BE, Kulkarni M, Heilbron D, Drown D, Raskin S, Pullinger CR, et al. (2003). Genetic analysis of a polymorphism in the human apoA-V gene: effect on plasma lipids. *J Lipid Res*. 44(6):1167–73.

Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. (2002). Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation*. 105(24):2893–8.

Arkan MC, Hevener AL, Greten FR, Maeda S, Li Z-W, Long JM, et al. (2005). IKK-beta links inflammation to obesity-induced insulin resistance. *Nat Med*. 11(2):191–8.

Baker JL, Rotimi CN, Shriner D (2017). Human ancestry correlates with language and reveals that race is not an objective genomic classifier. *Sci Rep*. 7(1):1572.

Banks AS, Davis SM, Bates SH, Myers MG (2000). Activation of downstream signals by the long form of the leptin receptor. *J Biol Chem*. 275(19):14563–72.

Bartos DC, Anderson JB, Bastiaenen R, Johnson JN, Gollob MH, Tester DJ, et al. (2013). A KCNQ1 mutation causes a high penetrance for familial atrial fibrillation. *J Cardiovasc Electrophysiol*. 24(5):562–9.

Belkina AC, Denis GV (2010). Obesity genes and insulin resistance. *Curr Opin Endocrinol Diabetes Obes*. 17(5):472–7.

Bender N, Allemann N, Marek D, Vollenweider P, Waeber G, Mooser V, et al. (2011). Association between variants of the leptin receptor gene (LEPR) and overweight: a systematic review and an analysis of the CoLaus study. *PLoS ONE*. 6(10):e26157.

Berezina A, Belyaeva O, Berkovich O, Baranova E, Karonova T, Bazhenova E, et al. (2015). Prevalence, Risk Factors, and Genetic Traits in Metabolically Healthy and Unhealthy Obese Individuals. *Biomed Res Int*. 2015:548734.

Blüher M (2014). Are metabolically healthy obese individuals really healthy? *Eur J Endocrinol*. 171(6):R209-219.

Botto LD, Yang Q (2000). 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. *Am J Epidemiol*. 151(9):862–77.

Boumaiza I, Omezzine A, Rejeb J, Rebhi L, Ouedrani A, Ben Rejeb N, et al. (2012). Relationship Between Leptin G2548A and Leptin Receptor Q223R Gene Polymorphisms and Obesity and Metabolic Syndrome Risk in Tunisian Volunteers. *Genet Test Mol Biomarkers*. 16(7):726–33.

Brennan AM, Mantzoros CS (2006). Drug Insight: the role of leptin in human physiology and pathophysiology—emerging clinical applications. *Nat Clin Pract Endocrinol Metab*. 2(6):318.

Buono C, Binder CJ, Stavrakis G, Witztum JL, Glimcher LH, Lichtman AH (2005). T-bet deficiency reduces atherosclerosis and alters plaque antigen-specific immune responses. *Proc Natl Acad Sci USA*. 102(5):1596–601.

Calori G, Lattuada G, Piemonti L, Garancini MP, Ragogna F, Villa M, et al. (2011). Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care*. 34(1):210–5.

Camhi SM, Waring ME, Sisson SB, Hayman LL, Must A (2013). Physical Activity and Screen Time in Metabolically Healthy Obese Phenotypes in Adolescents and Adults. *J Obes*. 2013:e984613.

Caunt CJ, Keyse SM (2013). Dual-specificity MAP kinase phosphatases (MKPs). *FEBS J*. 280(2):489–504.

Cha S, Yu H, Park AY, Song KH (2014). Effects of apolipoprotein A5 haplotypes on the ratio of

triglyceride to high-density lipoprotein cholesterol and the risk for metabolic syndrome in Koreans. *Lipids Health Dis.* 13:45. doi: 10.1186/1476-511X-13-45.

Chandran M, Phillips SA, Ciaraldi T, Henry RR (2003). Adiponectin: more than just another fat cell hormone? *Diabetes Care*. 26(8):2442–50.

Chang C-S, Lu Y-J, Chang H-H, Hsu S-H, Kuo P-H, Shieh C-C, et al. (2018). Role of adiponectin gene variants, adipokines and hydrometry-based percent body fat in metabolically healthy and abnormal obesity. *Obes Res Clin Pract*. 12(Suppl 2):49–61.

Chen Z, Zhang X, Ma G, Qian Q, Yao Y (2010). Association study of four variants in KCNQ1 with type 2 diabetes mellitus and premature coronary artery disease in a Chinese population. *Mol Biol Rep*. 37(1):207–12.

Chiodini BD, Specchia C, Gori F, Barlera S, D'Orazio A, Pietri S, et al. (2010). Adiponectin gene polymorphisms and their effect on the risk of myocardial infarction and type 2 diabetes: an association study in an Italian population. *Ther Adv Cardiovasc Dis*. 4(4):223–30.

Christodoulou A, Ierodiakonou D, Awofala AA, Petrou M, Kales SN, Christiani DC, et al. (2020). Variants in ADIPOQ gene are linked to adiponectin levels and lung function in young males independent of obesity. *PLoS ONE*. 15(1):e0225662.

Cohen SS, Gammon MD, Signorello LB, North KE, Lange EM, Fowke JH, et al. (2011). Serum adiponectin in relation to body mass index and other correlates in black and white women. *Ann Epidemiol*. 21(2):86–94.

Cuchel M, Wolfe ML, deLemos AS, Rader DJ (2002). The frequency of the cholesteryl ester transfer protein-TaqI B2 allele is lower in African Americans than in Caucasians. *Atherosclerosis*. 163(1):169–74.

Daghestani M, Purohit R, Daghestani M, Daghistani M, Warsy A (2019). Molecular dynamic (MD) studies on Gln233Arg (rs1137101) polymorphism of leptin receptor gene and associated variations in the anthropometric and metabolic profiles of Saudi women. *PLoS ONE*. 14(2):e0211381.

Damanhoury S, Newton AS, Rashid M, Hartling L, Byrne JLS, Ball GDC (2018). Defining metabolically healthy obesity in children: a scoping review. *Obes Rev*. 19 (11):1476–1491. doi: 10.1111/obr.12721.

Deboer MD (2011). Ethnicity, obesity and the metabolic syndrome: implications on assessing risk and targeting intervention. *Expert Rev Endocrinol Metab*. 6(2):279–89.

Dobbins M, Decorby K, Choi BCK (2013). The association between obesity and cancer risk: a meta-analysis of observational studies from 1985 to 2011. *ISRN Prev Med*. 2013:680536.

El Shafie MK, Esam El Din ISR, El Shazly RMA, Rageh TM, Alhanafy AM, El SAAE-R. (2017). C677T single-nucleotide polymorphism of methylenetetrahydrofolate reductase gene and colorectal cancer. *Menoufia Medical Journal*. 30(4):1057.

Fernández-Rhodes L, Young KL, Lilly AG, Raffield LM, Highland HM, Wojcik GL, *et al.* (2020). Importance of Genetic Studies of Cardiometabolic Disease in Diverse Populations. *Circulation Research*. 126(12):1816–1840.

Ferrante AW. (2013). The Immune Cells in Adipose Tissue. *Diabetes Obes Metab*. 15(0 3):34–8.

Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. (2009). Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med* 15(8):930–9

Forouhi NG, Sattar N (2006). CVD risk factors and ethnicity--a homogeneous relationship? *Atheroscler Suppl*. 7(1):11–9.

Fosmo AL, Skraastad ØB. (2017). The Kv7 Channel and Cardiovascular Risk Factors. *Front Cardiovasc Med*. 4:75.

Friend A, Craig L, Turner S. (2013). The prevalence of metabolic syndrome in children: a systematic review of the literature. *Metab Syndr Relat Disord*. 11(2):71–80.

Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, et al. (2007). Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell*. 131(1):33–45.

Genovesi S, Antolini L, Orlando A, Gilardini L, Bertoli S, Giussani M, et al. (2020). Cardiovascular Risk Factors Associated With the Metabolically Healthy Obese (MHO) Phenotype Compared to the Metabolically Unhealthy Obese (MUO) Phenotype in Children. *Front Endocrinol*. 11:27.

Gonzales MC, Yu P, Shiao SPK (2017). MTHFR Gene Polymorphism-Mutations and Air Pollution as Risk Factors for Breast Cancer. *Nurs Res*. 66(2):152–63.

González-Gil EM, Cadenas-Sanchez C, Santabárbara J, Bueno-Lozano G, Iglesia I, Gonzalez-Gross M, et al. (2018). Inflammation in metabolically healthy and metabolically abnormal adolescents: The HELENA study. *Nutr Metab Cardiovasc Dis*. 28(1):77–83.

Grallert H, Sedlmeier E-M, Huth C, Kolz M, Heid IM, Meisinger C, et al. (2007). APOA5 variants and metabolic syndrome in Caucasians. *J Lipid Res*. 48(12):2614–2621.

Grosskopf I, Baroukh N, Lee S-J, Kamari Y, Harats D, Rubin EM, et al. (2005). Apolipoprotein A-V deficiency results in marked hypertriglyceridemia attributable to decreased lipolysis of triglyceride-rich lipoproteins and removal of their remnants. *Arterioscler Thromb Vasc Biol*. 25(12):2573–9.

Gudnason V, Kakko S, Nicaud V, Savolainen MJ, Kesäniemi YA, Tahvanainen E, et al. (1999). Cholesteryl ester transfer protein gene effect on CETP activity and plasma high-density lipoprotein in European populations. *Eur J Clin Invest*. 29(2):116–128.

Guerrero-Romero F, Rodriguez-Moran M (2013). Serum magnesium in the metabolically-obese normal-weight and healthy-obese subjects. *Eur J Intern Med*. 24(7):639–43.

Hajer GR, van der Graaf Y, Olijhoek JK, Verhaar MC, Visseren FLJ (2007). Levels of homocysteine are increased in metabolic syndrome patients but are not associated with an increased cardiovascular risk, in contrast to patients without the metabolic syndrome. *Heart*. 93(2):216–20.

Hajjar RJ, Hulot J-S (2014). Modeling CVD in human pluripotent cells by genome editing. *J Am Coll Cardiol*. 64(5):460–2.

Halalkhor S, Jalali F, Tilaki KH, Shojaei S (2014). Association of two common polymorphisms of apolipoprotein A5 gene with metabolic syndrome indicators in a North Iranian population, a cross-sectional study. *J Diab Metab Disord*. 13:48. doi: 10.1186/2251-6581-13-48.

Hamer M, Batty GD, Kivimaki M (2012). Risk of future depression in people who are obese but metabolically healthy: The English Longitudinal Study of Ageing. *Mol Psychiatry*. 17(9):940–5.

Hausenloy DJ, Yellon DM (2008). Targeting residual cardiovascular risk: raising high-density lipoprotein cholesterol levels. *Heart*. 94(6):706–714.

Hegele RA, Tully C, Young TK, Connelly PW (1997). V677 mutation of methylenetetrahydrofolate reductases and cardiovascular disease in Canadian Inuit. *Lancet*. 349(9060):1221–2.

Heim N, Snijder MB, Heymans MW, Deeg DJH, Seidell JC, Visser M (2011). Optimal cutoff values for high-risk waist circumference in older adults based on related health outcomes. *Am J Epidemiol*. 174(4):479–89.

Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna JM (2016). Why are there race/ethnic differences in adult body mass index–adiposity relationships? A quantitative critical review. *Obes Rev*. 17(3):262–75.

Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, et al. (2002). A central role for JNK in obesity and insulin resistance. *Nature*. 420(6913):333.

Holmkvist J, Banasik K, Andersen G, Unoki H, Jensen TS, Pisinger C, et al. (2009). The type 2 diabetes associated minor allele of rs2237895 KCNQ1 associates with reduced insulin release following an oral glucose load. *PLoS ONE*. 4(6):e5872.

Hsu L-A, Ko Y-L, Hsu K-H, Ko Y-H, Lee Y-S (2002). Genetic variations in the cholesteryl ester transfer protein gene and high density lipoprotein cholesterol levels in Taiwanese Chinese. *Hum Genet*. 110(1):57–63.

Huang T, Ren J, Huang J, Li D (2013). Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach. *BMC Genomics*. 14:867.

Jang Y, Chae JS, Koh SJ, Hyun YJ, Kim JY, Jeong YJ, et al. (2008). The influence of the adiponectin gene on adiponectin concentrations and parameters of metabolic syndrome in non-diabetic Korean women. *Clin Chim Acta*. 391(1–2):85–90.

Jiang CQ, Liu B, Cheung BM, Lam TH, Lin JM, Li Jin Y, et al. (2010). A single nucleotide polymorphism in APOA5 determines triglyceride levels in Hong Kong and Guangzhou Chinese. *Eur J Hum Genet*. 18(11):1255–60.

Kanu JS, Qiu S, Cheng Y, Li R, Kou C, Gu Y, et al. (2018). Associations between three common single nucleotide polymorphisms (rs266729, rs2241766, and rs1501299) of ADIPOQ and cardiovascular disease: a meta-analysis. *Lipids Health Dis*. 17(1):126.

Karelis AD, Brochu M, Rabasa-Lhoret R (2004). Can we identify metabolically healthy but obese individuals (MHO)? *Diabetes Metab*. 30(6):569–72.

Kark JD, Sinnreich R, Leitersdorf E, Friedlander Y, Shpitzen S, Luc G (2000). Taq1B CETP polymorphism, plasma CETP, lipoproteins, apolipoproteins and sex differences in a Jewish population sample characterized by low HDL-cholesterol. *Atherosclerosis*. 151(2):509–518.

Kashani Farid MA, Azizi F, Hedayati M, Daneshpour MS, Shamshiri AR, Siassi F (2010). Association between CETP Taq1B and LIPC -514C/T polymorphisms with the serum lipid levels in a group of Tehran's population: a cross sectional study. *Lipids Health Dis*. 9:96. doi: 10.1186/1476-511X-9-96.

Khokhar A, Chin V, Perez-Colon S, Farook T, Bansal S, Kochummen E, et al. (2017). Differences between Metabolically Healthy vs Unhealthy Obese Children and Adolescents. *J Nat Med Assoc*. 109(3):203–10.

Krishnadath ISK, Toelsie JR, Hofman A, Jaddoe VWV (2016). Ethnic disparities in the prevalence of metabolic syndrome and its risk factors in the Suriname Health Study: a cross-sectional population study. *BMJ Open*. 6(12):e013183.

Kumar A. (2019). The impact of obesity on cardiovascular disease risk factor. *Asian J Med Sci.* 10(1):1–12. doi.org/10.3126/ajms.v10i1.21294

Lenz A, Diamond FB (2008). Obesity: the hormonal milieu. *Curr Opin Endocrinol Diabetes Obes*. 15(1):9–20.

Li L, Hu B, Gong S, Yan J (2011). Homocysteine-Induced Caspase-3 Activation by Endoplasmic Reticulum Stress in Endothelial Progenitor Cells from Patients with Coronary Heart Disease and Healthy Donors. *Biosci Biotechnol Biochem*. 75(7):1300–5.

Li R-K, Guo J (2014). Single nucleotide variances can account for loss of microRNA function: the emerging cross talk between genetics and epigenetics. *J Am Coll Cardiol*. 64(3):278–80.

Li Y, Wang X, Lu X (2014). KCNQ1 rs2237892 C→T gene polymorphism and type 2 diabetes mellitus in the Asian population: a meta-analysis of 15,736 patients. *J Cell Mol Med*. 18(2):274–82.

Lin E, Kuo P-H, Liu Y-L, Yang AC, Kao C-F, Tsai S-J (2016). Association and interaction of APOA5, BUD13, CETP, LIPA and health-related behavior with metabolic syndrome in a Taiwanese population. *Sci Rep*. 6:36830.

Lin H, Zhang L, Zheng R, Zheng Y (2017). The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article. *Medicine (Baltimore)*. 96(47):e8838.

Liu C, Wang C, Guan S, Liu H, Wu X, Zhang Z, et al. (2019). The Prevalence of Metabolically Healthy and Unhealthy Obesity according to Different Criteria. *Obes Facts*. 12 (1):78–90.

Liu Y, Wang C, Chen Y, Yuan Z, Yu T, Zhang W, et al. (2018). A variant in KCNQ1 gene predicts metabolic syndrome among northern urban Han Chinese women. *BMC Med Genet.* 19(1):153.

Lu Y, Tayebi N, Li H, Saha N, Yang H, Heng C-K (2013). Association of CETP Taq1B and -629C > A polymorphisms with coronary artery disease and lipid levels in the multi-ethnic Singaporean population. *Lipids Health Dis*. 12:85. doi: 10.1186/1476-511X-12-85.

Lüscher TF, von Eckardstein A, Simic B (2012). Therapeutic targets to raise HDL in patients at risk or with coronary artery disease. *Curr Vasc Pharmacol*. 10(6):720–4.

Maasz A, Kisfali P, Horvatovich K, Mohás M, Markó L, Csöngei V, et al. (2007). Apolipoprotein A5 T-1131C variant confers risk for metabolic syndrome. *Pathol Oncol Res.* 13(3):243–247.

Maász A, Kisfali P, Horvatovich K, Mohás M, Markó L, Csöngei V, et al. (2007). Apolipoprotein A5 T-1131C variant confers risk for metabolic syndrome. *Pathol Oncol Res*. 13(3):243–7.

Mabuchi H, Nohara A, Inazu A (2014). Cholesteryl Ester Transfer Protein (CETP) Deficiency and CETP Inhibitors. *Mol Cells*. 37(11):777–84.

Margolis-Gil M, Yackobovitz-Gavan M, Phillip M, Shalitin S (2018). Which predictors differentiate between obese children and adolescents with cardiometabolic complications and those with metabolically healthy obesity? *Pediatr Diabetes.* 19(7):1147–55.

Meigs JB, Wilson PWF, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. (2006). Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 91(8):2906–12.

Melistas L, Mantzoros CS, Kontogianni M, Antonopoulou S, Ordovas JM, Yiannakouris N (2009). Association of the +45T>G and +276G>T polymorphisms in the adiponectin gene with insulin resistance in nondiabetic Greek women. *Eur J Endocrinol*. 161(6):845–52.

Mente A, Razak F, Blankenberg S, Vuksan V, Davis AD, Miller R, et al. (2010). Ethnic Variation in Adiponectin and Leptin Levels and Their Association With Adiposity and Insulin Resistance. *Diabetes Care*. 33(7):1629–34.

Menzaghi C, Trischitta V, Doria A. (2007). Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes*. 56(5):1198–209.

Merkel M, Loeffler B, Kluger M, Fabig N, Geppert G, Pennacchio LA, et al. (2005). Apolipoprotein AV accelerates plasma hydrolysis of triglyceride-rich lipoproteins by interaction with proteoglycan-bound lipoprotein lipase. *J Biol Chem.* 280(22):21553–60.

Misra A, Khurana L (2009). The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metab Syndr Relat Disord*. 7(6):497–514.

Misra A, Vikram NK (2004). Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition*. 20(5):482–91.

Munisamy M, Al-Gahtany M, Tripathi M, Subbiah V (2015). Impact of MTHFR (C677T) gene polymorphism on antiepileptic drug monotherapy in North Indian epileptic population. *Ann Saudi Med*. 35(1):51–7.

Muñoz-Garach A, Cornejo-Pareja I, Tinahones FJ (2016). Does metabolically healthy obesity exist? *Nutrients*. 8(6):320.

Nasreddine L, Tamim H, Mailhac A, AlBuhairan FS (2018). Prevalence and predictors of metabolically healthy obesity in adolescents: findings from the national "Jeeluna" study in Saudi-Arabia. *BMC Pediatr*. 18:281.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment

Panel III). (2001). Executive Summary of the Third Report. *JAMA*. 285(19):2486–97.

Nonn L, Duong D, Peehl DM (2007). Chemopreventive anti-inflammatory activities of curcumin and other phytochemicals mediated by MAP kinase phosphatase-5 in prostate cells. *Carcinogenesis*. 28(6):1188–96.

Nowzari Z, Masoumi M, Nazari-Robati M, Akbari H, Shahrokhi N, Asadikaram G (2018). Association of polymorphisms of leptin, leptin receptor and apelin receptor genes with susceptibility to coronary artery disease and hypertension. *Life Sci*. 207:166–71.

O'Rourke RW, White AE, Metcalf MD, Winters BR, Diggs BS, Zhu X, et al. (2012). Systemic inflammation and insulin sensitivity in obese IFN-γ knockout mice. *Metab Clin Exp.* 61(8):1152–61.

Okada T, Ohzeki T, Nakagawa Y, Sugihara S, Arisaka O, Study Group of Pediatric Obesity and Its related Metabolism (2010). Impact of leptin and leptin-receptor gene polymorphisms on serum lipids in Japanese obese children. *Acta Paediatr*. 99(8):1213–7.

Olofsson S-O (2005). ApoA-V: the regulation of a regulator of plasma triglycerides. Arterioscler Thromb Vasc Biol. 25(6):1097–9.

Ong KL, Jiang CQ, Liu B, Jin YL, Tso AW, Tam S, et al. (2011). Association of a genetic variant in the apolipoprotein A5 gene with the metabolic syndrome in Chinese. *Clin Endocrinol*. 74(2):206–213.

Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A, et al. (2000). Association of cholesteryl ester transfer protein–Taq IB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham study. *Arterioscler Thromb Vasc Biol.* 20(5):1323–1329.

Pajvani UB, Scherer PE (2003). Adiponectin: systemic contributor to insulin sensitivity. Curr Diab Rep. 3(3):207–213.

Pepe G, Camacho Vanegas O, Giusti B, Brunelli T, Marcucci R, Attanasio M, et al. (1998). Heterogeneity in world distribution of the thermolabile C677T mutation in 5,10-methylenetetrahydrofolate reductase. *Am J Hum Genet*. 63(3):917–20.

Prince RL, Kuk JL, Ambler KA, Dhaliwal J, Ball GD (2014). Predictors of metabolically healthy obesity in children. *Diabetes care.* 37(5):1462-8.

Qi Q, Li H, Loos RJF, Liu C, Wu Y, Hu FB, et al. (2009). Common variants in KCNQ1 are associated with type 2 diabetes and impaired fasting glucose in a Chinese Han population. *Hum Mol Genet*. 18(18):3508–15.

Ragin CC, Dallal C, Okobia M, Modugno F, Chen J, Garte S, et al. (2009). Leptin levels and leptin receptor polymorphism frequency in healthy populations. *Infect Agents Cancer*. 4 Suppl 1:S13.

Rahman M, Temple JR, Breitkopf CR, Berenson AB (2009). Racial differences in body fat distribution among reproductive-aged women. *Metab Clin Exp.* 58(9):1329–37.

Real JT, Martinez-Hervas S, Garcia-Garcia AB, Chaves FJ, Civera M, Ascaso JF, et al. (2009). Association of C677T polymorphism in MTHFR gene, high homocysteine and low HDL cholesterol plasma values in heterozygous familial hypercholesterolemia. *J Atheroscler Thromb.* 16(6):815–20.

Reinehr T, Wolters B, Knop C, Lass N, Holl RW (2015). Strong effect of pubertal status on metabolic health in obese children: a longitudinal study. *J Clin Endocrinol Metab*. 100(1):301–308.

Rejeb J, Omezzine A, Rebhi L, Naffeti I, Kchok K, Belkahla R, et al. (2008). Association of the cholesteryl ester transfer protein Taq1 B2B2 genotype with higher high-density lipoprotein cholesterol concentrations and lower risk of coronary artery disease in a Tunisian population. *Arch Cardiovasc Dis*. 101(10):629–36.

Remor JM, Lopes WA, Locateli JC, Oliveira RP, Simões CF, Barrero CAL, et al. (2019). Prevalence of metabolically healthy obese phenotype and associated factors in South American overweight adolescents: A cross-sectional study. *Nutrition*. 60:19–24.

Rey-López JP, de Rezende LF, Pastor-Valero M, Tess BH (2014). The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used: Prevalence of metabolically healthy obesity. *Obes Rev*. 15(10):781–90.

Ridker PM, Paré G, Parker AN, Zee RYL, Miletich JP, Chasman DI (2009). Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genomewide analysis among 18 245 initially healthy women from the Women's Genome Health Study. *Circ Cardiovasc Genet*. 2(1):26–33.

Robinson K, Prins J, Venkatesh B (2011). Clinical review: adiponectin biology and its role in inflammation and critical illness. *Crit Care*. 15(2):221.

Rosengren AH, Braun M, Mahdi T, Andersson SA, Travers ME, Shigeto M, et al. (2012). Reduced insulin exocytosis in human pancreatic β-cells with gene variants linked to type 2 diabetes. Diabetes. 61(7):1726–33.

Ruan H, Dong LQ (2016). Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol*. 8(2):101–9.

Saukko M, Kesäniemi YA, Ukkola O (2010). Leptin receptor Lys109Arg and Gln223Arg polymorphisms

are associated with early atherosclerosis. *Metab Syndr Relat Disord*. 8(5):425–430.

Schlauch KA, Kulick D, Subramanian K, De Meirleir KL, Palotás A, Lombardi VC (2019). Single-nucleotide polymorphisms in a cohort of significantly obese women without cardiometabolic diseases. *Int J Obes*. 43(2):253-262.

Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG (2000). Central nervous system control of food intake. *Nature*. 404(6778):661–71.

Scott RA, Scott LJ, Mägi R, Marullo L, Gaulton KJ, Kaakinen M, et al. (2017). An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. *Diabetes*. 66(11):2888–902.

Sims EA (2001). Are there persons who are obese, but metabolically healthy? *Metab Clin Exp*. 50 (12):1499–504.

Song J, Yoon SR, Kim OY (2018). T allele at ADIPOQ rs1501299 G/T polymorphism is more susceptible to the influence of circulating adiponectin on arterial stiffness in nondiabetic men. *Diabetol Metab Syndr*. 10(1):44.

Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, García-Fuentes E, Almaraz MC, Colomo N, et al. (2013). Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. *J Clin Endocrinol Metab*. 98(6):2318–25.

Stolarczyk E, L ord GM, Howard JK (2014). The immune cell transcription factor T-bet. *Adipocyte*. 3(1):58–62.

Stolarczyk E, Vong CT, Perucha E, Jackson I, Cawthorne MA, Wargent ET, et al. (2013). Improved Insulin Sensitivity despite Increased Visceral Adiposity in Mice Deficient for the Immune Cell Transcription Factor T-bet. *Cell Metab.* 17(4):520–33.

Su X, Kong Y, Peng D (2018). New insights into apolipoprotein A5 in controlling lipoprotein metabolism in obesity and the metabolic syndrome patients. *Lipids Health Dis*. 17(1):174. doi: 10.1186/s12944-018-0833-2.

Szabo SJ, Sullivan BM, Stemmann C, Satoskar AR, Sleckman BP, Glimcher LH (2002). Distinct effects of T-bet in TH1 lineage commitment and IFN-gamma production in CD4 and CD8 T cells. *Science*. 295(5553):338–42.

Tailor AM, Peeters PHM, Norat T, Vineis P, Romaguera D. (2010). An update on the prevalence of the metabolic syndrome in children and adolescents. *Int J Pediatr Obes.* 5(3):202–13.

Tang P, Low HB, Png CW, Torta F, Kumar JK, Lim HY, et al. (2019). Protective Function of Mitogen-Activated Protein Kinase Phosphatase 5 in Aging- and Diet-Induced Hepatic Steatosis and Steatohepatitis. *Hepatology Communications*. 3(6):748–62.

Taniguchi Y (2016). The Bromodomain and Extra-Terminal Domain (BET) Family: Functional Anatomy of BET Paralogous Proteins. *Int J Mol Sci*. 17(11):pii:E1849.

Thompson A, Di Angelantonio E, Sarwar N, Erqou S, Saleheen D, Dullaart RPF, et al. (2008). Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. *JAMA*. 299(23):2777–88.

Trimmer EE (2013). Methylenetetrahydrofolate reductase: biochemical characterization and medical significance. *Curr Pharm Des*. 19(14):2574–93.

Turki A, Mtiraoui N, Al-Busaidi AS, Khirallah M, Mahjoub T, Almawi WY (2012). Lack of association between genetic polymorphisms within KCNQ1 locus and type 2 diabetes in Tunisian Arabs. *Diabetes Res Clin Pract.* 98(3):452–8.

Upadhyay J, Farr O, Perakakis N, Ghaly W, Mantzoros C (2018). Obesity as a disease. *Medical Clinics.* 102(1):13–33.

Vong QP, Leung W-H, Houston J, Li Y, Rooney B, Holladay M, et al. (2014). TOX2 regulates human natural killer cell development by controlling T-BET expression. *Blood*. 124(26):3905–13.

Walker SE, Gurka MJ, Oliver MN, Johns DW, DeBoer MD (2012). Racial/ethnic discrepancies in the metabolic syndrome begin in childhood and persist after adjustment for environmental factors. *Nutr Metab Cardiovasc Dis*. 22(2):141–8.

Walther TC, Farese RV (2012). Lipid droplets and cellular lipid metabolism. *Annu Rev Biochem*. 81:687–714.

Wan L, Li Y, Zhang Z, Sun Z, He Y, Li R (2018). Methylenetetrahydrofolate reductase and psychiatric diseases. *Translational Psychiatry*. 8:242.

Wang B, Zhuang R, Luo X, Yin L, Pang C, Feng T, et al. (2015). Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. *Horm Metab Res*. 47(11):839–845.

Wang F, Deeney JT, Denis GV (2013). Brd2 gene disruption causes 'metabolically healthy' obesity: Epigenetic and chromatin-based mechanisms that uncouple obesity from Type 2 diabetes. *Vitam Horm*. 91:49–75.

Wang F, Liu H, Blanton WP, Belkina A, Lebrasseur NK, Denis GV (2009). Brd2 disruption in mice causes severe obesity without Type 2 diabetes. *Biochem J*. 425(1):71–83.

Wang J, Wang LJ, Zhong Y, Gu P, Shao JQ, Jiang SS, et al. (2013). CETP gene polymorphisms and risk of coronary atherosclerosis in a Chinese population. *Lipids Health Dis*. 12(1):176.

Wang J, Xu L, Xia H, Li Y, Tang S (2018). Association of MTHFR C677T gene polymorphism with metabolic syndrome in a Chinese population: a case–control study. *J Int Med Res*. 46(7):2658.

Ward M, Wilson CP, Strain JJ, Horigan G, Scott JM, McNulty H. (2011). B-vitamins, methylenetetrahydrofolate reductase (MTHFR) and hypertension. *Int J Vitam Nutr Res*. 81(4):240–4.

Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. (2008). The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med*. 168 (15):1617–24.

World Health Organization. Obesity and Overweight. Fact sheet no 3 March 2020. https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 18 Mar 2020.

World Health Organization. (2011). Waist circumference and waist-hip ratio. Report of a WHO Expert Consultation. Geneva, 8–11 December 2008. Geneva: World Health Organization.

Xu C, Bai R, Zhang D, Li Z, Zhu H, Lai M, et al. (2013). Effects of APOA5- 1131T> C (rs662799) on fasting plasma lipids and risk of metabolic syndrome: evidence from a case-control study in China and a meta-analysis. *PLoS ONE*. 8(2):e56216.

Xuan C, Bai X-Y, Gao G, Yang Q, He G-W (2011). Association between polymorphism of methylenetetrahydrofolate reductase (MTHFR) C677T and risk of myocardial infarction: a meta-analysis for 8,140 cases and 10,522 controls. *Arch Med Res*. 42(8):677–85.

Yadav U, Kumar P, Gupta S, Rai V. (2017). Distribution of MTHFR C677T Gene Polymorphism in Healthy North Indian Population and an Updated Meta-analysis. Indian J *Clin Biochem*. 32(4):399–410.

Yamada Y, Kato K, Hibino T, Yokoi K, Matsuo H, Segawa T, et al. (2007). Prediction of genetic risk for metabolic syndrome. *Atherosclerosis*. 191(2):298–304.

Yang MM, Wang J, Fan JJ, Ng TK, Sun DJ, Guo X, et al. (2016). Variations in the obesity gene "LEPR" contribute to risk of type 2 diabetes mellitus: evidence from a meta-analysis. *J. Diab Res*. 2016. 5412084.

Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, et al. (2008). Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet*. 40(9):1092–7.

Yavuz EN, Ozdemir O, Catal S, Bebek N, Ozbek U, Baykan B (2012). Bromodomain-Containing Protein 2 gene in photosensitive epilepsy. *Seizure*. 21(8):646–648.

Ye H, Zhou A, Hong Q, Tang L, Xu X, Xin Y, et al. (2015). Positive Association between APOA5 rs662799 Polymorphism and Coronary Heart Disease: A Case-Control Study and Meta-Analysis. *PLoS ONE*. 10(8):e0135683.

Yoon DY, Lee YA, Lee J, Kim JH, Shin CH, Yang SW (2017). Prevalence and Clinical Characteristics of Metabolically Healthy Obesity in Korean Children and Adolescents: Data from the Korea National Health and Nutrition Examination Survey. *J Korean Med Sci*. 32(11):1840–1847.

Yuan H-P, Sun L, Li X-H, Che F-G, Zhu X-Q, Yang F, et al. (2016). Association of Adiponectin Polymorphism with Metabolic Syndrome Risk and Adiponectin Level with Stroke Risk: A Meta-Analysis. *Sci Rep*. 6:31945.

Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, et al. (2001). High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. *Nat Med*. 7(7):853–7.

Zadjali F, AL-Yahyaee S, Hassan MO, Albarwani S, Bayoumi RA (2013). Association of adiponectin promoter variants with traits and clusters of metabolic syndrome in Arabs: Family-based study. *Gene*. 527 (2):663–9.

Zhang T, Li X, Du Q, Gong S, Wu M, Mao Z, et al. (2014). DUSP10 gene polymorphism and risk of colorectal cancer in the Han Chinese population. *Eur J Cancer Prev*. 23(3):173–6.

Zhang W, Wang H, Guan X, Niu Q, Li W (2015). Variant rs2237892 of KCNQ1 Is Potentially Associated with Hypertension and Macrovascular Complications in Type 2 Diabetes Mellitus in A Chinese Han Population. *Genomics Proteomics Bioinformatics*. 13(6):364–70.

Zhang Y, Nguyen T, Tang P, Kennedy NJ, Jiao H, Zhang M, et al. (2015). Regulation of Adipose Tissue Inflammation and Insulin Resistance by MAPK Phosphatase 5. *J Biol Chem*. 290(24):14875–83.

Zhou JM, Zhang M, Wang S, Wang BY, Han CY, Ren YC, et al. (2016). Association of the ADIPOQ Rs2241766 and Rs266729 Polymorphisms with Metabolic Syndrome in the Chinese Population: A Meta-analysis. *Biomed Environ Sci*. 29(7):505–15.

Zhu B, Wu X, Zhi X, Liu L, Zheng Q, Sun G (2014). Methylenetetrahydrofolate reductase C677T polymorphism and type 2 diabetes mellitus in Chinese population: a meta-analysis of 29 case-control studies. *PLoS ONE*. 9(7):e102443.

Zhu W, Wang C, Liang L, Shen Z, Fu J, Liu P, et al. (2014). Triglyceride-raising APOA5 genetic variants are associated with obesity and non-HDL-C in Chinese children and adolescents. *Lipids Health Dis.* 13(1):93. doi: 10.1186/1476-511X-13-93.

Zimmet P, Alberti KGM, Kaufman F, Tajima N, Silink M, Arslanian S, et al. (2007). The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes.* 8(5):299–306.