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Identifying metabolic syndrome in a clinical cohort: Implications for prevention of chronic disease☆

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ABSTRACT

In the clinical setting, calculating cardiovascular disease (CVD) risk is commonplace but the utility of the harmonised equation for metabolic syndrome (MetS) (Alberti et al., 2009) is less well established. The aims of this study were to apply this equation to an overweight clinical cohort to identify risk factors for being metabolically unhealthy and explore associations with chronic disease.

Baseline data were analysed from a lifestyle intervention trial of Illawarra residents recruited in 2014/2015. Participants were aged 25–54 years with a BMI 25–40 kg/m^2. Data included MetS, CVD risk, insulin sensitivity, weight, body fat, diet, peripheral artery disease (PAD), physical activity, socio-economic position and psychological profile. Backward stepwise regression tested the association of covariates with MetS status and linear or logistic regression tested associations between MetS and risk of CVD, coronary heart disease, PAD and insulin resistance. 374 participants were included in the analysis with 127 (34.0%) categorised with MetS. Covariates significantly and positively associated with MetS were higher BMI (odds 1.26, $p < 0.01$) and older age (odds 1.08, $p < 0.01$). MetS participants ($n = 351$) had a 4.50% increase in CVD risk and were 8.1 and 12.7 times (respectively) more likely to be at risk of CHD and insulin resistance, compared to participants without MetS.

The utility of the harmonised equation in the clinical setting was confirmed in this overweight clinical cohort. Those classified as having MetS were more likely to be older, overweight/obese individuals and they had a substantially higher risk of developing CVD and insulin resistance than those without MetS.

1. Introduction

A decline in metabolic health often precedes cardiovascular disease (CVD)[1] and diabetes mellitus, so there are benefits in early identification and intervention. Definitions of "metabolically unhealthy" vary. Investigators have frequently used either the absence of metabolic syndrome (MetS), high insulin sensitivity, or a combination of both to define metabolic health in overweight or obese individuals (Hinnouho et al., 2013; Ärnlöv et al., 2010). A global definition of MetS now exists (Alberti et al., 2009) that unifies previously published equations with an agreement that central obesity is not an obligatory component. The harmonised definition of MetS is defined as having three of the following: elevated waist circumference (country specific guidelines), triglycerides ≥1.7 mmol/L*, systolic blood pressure ≥130 or diastolic ≥85 mm Hg*, glucose ≥100 mg/dL and reduced HDL cholesterol <1.0 mmol/L (males) or <1.3 mmol/L (females) (or drug treatment as indicated*) (Alberti et al., 2009). Recently published studies have also been found to use previous MetS equations (Hinnouho et al., 2013; Shab-Bidar et al., 2014; de Castro and Scorsatto, 2015). While risk calculations of CVD are readily available (D'Agostino et al., 2008; Wilson et al., 1998), the identification of MetS is not commonly used in practice and could help initiate early intervention for disease prevention.

MetS often occurs in the presence of obesity which is known to cause a decline in life expectancy due to its associated metabolic and cardiovascular comorbid disorders. Clinical practice guidelines for obesity defer to treatment with diet, physica activity and behavioural support (Council NHaMR, 2013). However, recent research suggests that not all obese individuals have the same metabolic risk profile (Phillips, 2013) and this has implications for personalising treatment. In the first instance it may be relevant to distinguish individuals at high risk for obesity-related metabolic diseases by identifying the presence of MetS.

In addition to traditional risk factors such as obesity, many other factors have been suggested as being associated with MetS, such as chronic stress (Epel et al., 2004); socioeconomic position (Brunner et al., 1997); cardiorespiratory fitness (LaMonte et al., 2005), peripheral artery

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[1] List of abbreviations: metabolic syndrome (MetS), body mass index (BMI), ankle brachial index (ABI), systolic blood pressure (SBP), diastolic blood pressure (DBP), international physical activity questionnaire (IPAQ), depression anxiety stress scale (DASS-21), cardiovascular disease (CVD), coronary heart disease (CHD).

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disease (PAD) (Wild et al., 2006), and dietary saturated fatty acids (Shab-Bidar et al., 2014). These all have implications for the mode of treatment, particularly in relation to the nature of diet, exercise and psychological support.

The aims of this study were to apply the harmonised equation for calculation of MetS to a clinical cohort and to identify risk factors for being metabolically unhealthy, as well as assess presence of MetS and risk of chronic disease.

2. Methods

2.1. Study design and setting

This paper reports on a secondary analysis of data from the HealthTrack study, a 12 month healthy lifestyle randomised clinical trial. Participants were randomised to receiving either usual care (general advice), or individualised dietary advice with exercise prescription and health coaching, with or without a healthy food supplement (walnuts). Participants were recruited from the Illawarra region of NSW between May 2014 and April 2015. Inclusion criteria for the study were: permanent residents of the Illawarra region (NSW, Australia), adults aged 25–54 years, and with a body mass index (BMI) in the range 25–40 kg/m^2. Exclusion criteria were: unable to communicate in English; severe medical conditions, impaired ability to participate; suffering from immunodeficiency; reported illegal drug use or regular alcohol intake (>50 g/day). Ethical approval was granted by the University of Wollongong/Illawarra Shoalhaven Local Health District Human Research Ethics Committee (Health and Medical) (HE 13/189). Full written consent was obtained prior to study commencement. The study is registered with the ANZ Clinical Trial Registry (ANZCTRN12614000581662).

Full details of the protocol and methodology have previously been described (Tapsell et al., 2015). In summary, at baseline 377 participants had *body weight* (*kg*) and *%body fat* measured using scales with a bioelectrical impedance component. *Fasting blood lipids* (total cholesterol, LDL, HDL, triglycerides) and *blood glucose* were collected and tested through a registered pathology service (Southern IML Pathology). *Systolic* (*SBP*) *and diastolic blood pressure* (*DBP*) was measured using the Omron BP-203RPEIII VP-1000 device (Omron Health Care, Kyoto, Japan). Arterial stiffness (baPWV) and arterial occlusion (*ankle brachial index - ABI*) data were also collected from this device, giving a direct measure of peripheral artery disease. An ABI of <0.90 or >1.40 was classified as indicative of peripheral artery disease, ABI between 0.90 and 1.00 was classified as at risk of peripheral artery disease, and ABI between 1.01 and 1.39 was classified as healthy. *Dietary intake* was assessed using 4 day food records completed by participants, which included one weekend day. Dietary data was analysed using FoodWorks software (Version 7, 2012, Xyris Software, Spring Hill, QLD, Australia). Food intake data was converted to energy and macronutrient intake using the AUSNUT2007 food composition database (AUSNUT, 2007). *Physical activity* was assessed using the International Physical Activity Questionnaire (IPAQ) short form survey questions (Craig et al., 2003) and by a scientific grade pedometer (Yamax Digiwalker SW200, Pedometers Australia) worn for 4 consecutive days to confirm an average number of steps per day. *Psychological profile* was assessed using the Physical and Mental Quality of Life Assessment (SF-12) (Jenkinson et al., 2001) and the Depression Anxiety Stress Scale (DASS-21) (Lovibond SHaPFL, 1995). *Socio economic position* was approximated by the use of level of education attained and the average household income, which were both self-reported in an on-line population survey completed during screening for the randomised controlled trial. These covariates were included in the analysis as they are related to the three components of the lifestyle intervention which were implemented in the HealthTrack study after the baseline assessment, those being: dietary counselling, exercise advice and psychological coaching.

MetS was calculated using the harmonised definition (Alberti et al., 2009), with waist circumference thresholds set at the AHA/NHLBI (ATP III) levels of ≥102 cm for males and ≥88 cm for females. Participants were categorised as MUO if MetS was present or MHO if no MetS was present. Framingham CVD and coronary heart disease (CHD) risk were calculated based on the published CVD equations (D'Agostino et al., 2008) and CHD score sheets (Wilson et al., 1998). A risk percentage of <10% was categorised as 'low risk', and 10% or more were categorised as 'moderate to high risk' (<1% had a high risk of CVD and CHD, therefore moderate and high risk categories were combined). Similarly, for ABI the peripheral artery disease category (≤0.90) was combined with the at risk category (0.91–1.00) for analysis. Insulin resistance was defined as participants prescribed hypoglycaemic agents or a glycated haemoglobin (HbA1c) level >6%.

2.2. Statistical analysis

The statistical package used for analysis was IBM SPSS Statistics (version 21.0, IBM Corp, Chicago IL, 2012). Analyses included baseline data from all participants recruited into the HealthTrack study. The cross-sectional associations between physiological and lifestyle covariates and those classified as having MetS were analysed using backward stepwise logistic regression. Covariates included demographic (age, BMI, gender, % body fat); psychological (DASS-21, SF12 mental scale); physical activity (IPAQ, steps/day); dietary (total kilojoules, total fat, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA) and saturated fat); and social (education level, household income). Predictors which achieved a p value <0.2 in univariate analysis were assessed for inclusion in the multivariate model. The final model was checked using forward elimination (data not shown). Linear regression was used to examine associations between incidence of MetS and CVD risk, while logistic regression was used to test associations between MetS and CHD risk, peripheral artery disease and insulin resistance.

3. Results

Of the 377 participants randomised, data required for calculation of MetS was available for 374, and 127 participants (34.0%) were classified with MetS (Table 1). Multivariate analysis demonstrated that having a higher BMI (odds 1.26, $p < 0.01$) and older age (odds 1.08, $p < 0.01$) were significantly and positively associated with having MetS (Table 2). None of the other psychological, physical, dietary or social factors had a significant association with MetS classification.

To examine CVD and CHD estimated risk, data were available for $n = 351$ participants (Table 3). The median risk of experiencing cardiovascular disease within the next 10 years for all participants (interquartile range) was 3.89% (1.83–7.00). Most participants (88–92%) were in the low risk (<10%) category. Using linear regression, participants classified with MetS had a 4.50% increase in CVD risk compared to no-MetS participants (odds 4.50 (95% CI: 3.72, 5.28), $p < 0.01$). Using logistic regression, it was identified that MetS participants were 8.1 times more likely to be at risk of CHD than others (odds 8.07 (95% CI: 3.16, 20.62), $p < 0.01$).

A total of $n = 26$ (6.9%) of participants were categorised as being insulin resistant (15 on prescribed hypoglycaemic medication, 11 with HbA1c >6%). Using logistic regression, MetS participants were found to be 12.7 times more likely to be insulin resistant (odds 12.73 (95% CI: 4.28, 37.85), $p < 0.01$). In contrast, analysis of available data for MetS and ABI ($n = 372$) found that MetS did not significantly predict peripheral artery disease (odds 0.91 (95% CI: 0.55, 1.51), $p = 0.72$).

4. Discussion

Obesity is a public health problem that contributes significantly to the increasing prevalence of chronic diseases such as diabetes mellitus and CVD. However, given that metabolic risk may differ between obese individuals, the identification of those with MetS and the factors associated with this risk may assist in developing approaches to

Table 1
Baseline characteristics of Illawarra (NSW, Australia) participants.

Baseline characteristic	MetS (n = 127)	No MetS (n = 247)
Demographic		
Males/females (%)	33/67	23/77
Age (years)	45.8 ± 6.6	42.0 ± 8.5
Body mass index (kg/m^2)	35.1 ± 3.9	31.3 ± 3.8
Body fat (%) (n = 371)	42.4 ± 6.6	39.4 ± 7.2
Metabolic		
Systolic blood pressure (mm Hg)	135.0 ± 14.9	119.9 ± 12.7
HDL (mmol/L)	1.2 ± 0.3	1.5 ± 0.4
Total cholesterol (mmol/L)	5.4 ± 1.1	5.1 ± 0.9
Triglycerides (mmol/L)	1.8 ± 0.9	1.2 ± 1.3
Glucose (mmol/L)	6.0 ± 1.7	5.1 ± 0.6
Smoker/non-smoker (%) (n = 373)	5/95	4/96
Waist circumference (cm)	110.6 ± 10.3	99.9 ± 10.8
Psychological		
DASS depression (%high[a])	4.8 ± 4.3 (43.3)	4.0 ± 4.0 (34.8)
DASS anxiety (%high[a])	3.1 ± 3.2 (32.3)	2.6 ± 2.8 (25.9)
DASS stress (%high[a])	6.8 ± 3.9 (38.6)	6.5 ± 4.2 (37.2)
DASS total	14.6 ± 10.0	13.1 ± 9.2
SF 12 mental (n = 370)	46.3 ± 10.7	46.4 ± 9.6
Physical activity		
IPAQ (MetS) (n = 368)	1396.7 ± 1514.3	1391.7 ± 1414.6
Steps/day (n = 294)	7012.1 ± 3030.2	7931.5 ± 3042.2
Dietary		
Total energy (kJ) (n = 336)	9314.9 ± 2667.5	8861.6 ± 2343.9
Energy from fat (%) (n = 336)	34.7 ± 5.7	34.6 ± 5.0
MUFA (% of fat) (n = 336)	40.2 ± 4.8	40.6 ± 4.8
PUFA (% of fat) (n = 336)	16.4 ± 4.3	16.8 ± 4.6
Saturated fat (% of fat) (n = 336)	43.4 ± 6.7	42.6 ± 7.4
Social		
University/post grad degree (%)	42	55
Household income <$80,000 (%)	27	24
Household income $80–159,999 (%)	45	43
Household income >$160,000 (%)	15	20
Income not recorded (%)	13	14
Pharmacological		
Antihypertensive (%)	32.3	3.6
Hypolipidaemic (%)	15.0	5.3
Antidepressant/antianxiety (%)	22.0	14.2

Data are expressed as mean ± standard deviation or %.
[a] Proportion of high (including mild, moderate, severe and extremely severe) scores of depression ≥5, anxiety ≥4, and stress ≥8.

preventive services, especially since metabolic disturbances occur prior to the onset of chronic disease. These analyses provided some insights into who is at risk of having MetS and to what degree individuals with MetS increase their risk of developing chronic disease. The application of the harmonised equation proved useful in making this identification in an overweight clinical cohort that interestingly identified increased risk in developing CVD, CHD and insulin resistance but not PAD (as assessed using ABI). The latter may be due to the specificity of the measurement, and it was noted that most of the participants were at low risk of CVD. These results highlight the gaps between assessment of risk and the onset of disease, and this has implications for assessing outcomes for lifestyle intervention. While it is appropriate to identify at risk individuals and encourage lifestyle modification, a focus on behaviour changes and indications of reduced risk may be more appropriate than reduced disease incidence.

The importance of measuring MetS in individuals has not been confirmed, however as prevention programs aim to address individuals health issues before they develop into chronic disease, it may become a vital assessment tool. Interest in the metabolic syndrome was high between 1997 and 2005, however since the most recent definition was published in 2009 (Alberti et al., 2009), there appears to be a paucity of data utilising the harmonised definition. Our study included healthy participants aged between 25 and 54 years with a BMI in the range 24–40 kg/m^2. It is well documented that overweight/obesity is the most important precursor for development of MetS (Ma and Zhu, 2013), so our participants represented those at greatest risk of MetS and at a point of greatest benefit from lifestyle change, the primary treatment option. This sub-analysis of the HealthTrack clinical trial at baseline demonstrated that amongst the many factors included in the analysis, only older age and higher BMI predicted the presence of MetS, as classified by the harmonised equation. As the development of MetS begins with excess central adiposity, the findings were not surprising, due to the prevalence of abdominal obesity in older overweight individuals (Rutter et al., 2004). Still, our analysis confirms the results of previous studies that have reported BMI and age to be associated with MetS (Alexander et al., 2008) in large national surveys using the ATPIII criteria.

Those classified as MetS in this cohort were associated with a higher percentage risk of developing CHD or CVD within the next ten years and of developing diabetes mellitus; however we were not able to predict peripheral artery disease, as indicated by ABI. The diagnosis of MetS is reported to increase the risk of CVD by 30–400%, with the variation likely due to differing definitions, populations studied, and length of follow-up (Wannamethee et al., 2005; Lakka et al., 2002; Wilson et al., 2005). In our cohort characterised by a low prevalence of moderate-high CVD risk (7–11%), those diagnosed with MetS had a 4.50% increase in CVD risk and were eight times more likely to develop CHD within the next 10 years compared to participants without MetS. A low ABI has previously been reported in participants with MetS (Wild et al., 2006). We did not find an association between participants with MetS and low ABI, but our study only contained a small proportion of participants diagnosed with peripheral artery disease.

Insulin resistance was strongly associated with MetS in our analyses, with a 12.7 times greater risk compared to individuals without MetS. This finding is similar to another study examining obese subjects with MetS that reported an adjusted relative risk of 10.3 for diabetes (Meigs et al., 2006). These findings are expected as insulin resistance is strongly and positively associated with BMI, most likely due to increased liver and visceral fat content and the associated inflammatory signalling (Kantartzis et al., 2010).

We also examined other lifestyle factors. The effect of psychosocial stress on MetS appears to be reciprocal in that chronic stress induces MetS as well as the associated hormonal dysfunctions of MetS augment cortisol-induced stress (Brunner et al., 2002). More recently however, the GEA study indicated that self-reported chronic stress did not predict MetS (Ortega-Montiel et al., 2015). Our current analyses did not show any significant association between stress, anxiety, depression or quality of life and MetS. This may be due to the indirect methods used to assess mental health, which were similar to that used in the GEA study. In addition, Brunner et al. (2002) only demonstrated an association in male participants, whereas our study sample was predominantly female.

From a broader social perspective, lower social position has been suggested as increasing the probability of MetS (Brunner et al., 1997), as well as a low education level (Lee et al., 2005). In contrast, our analyses found neither education level nor household income were significantly associated with MetS. The difference could be explained in terms of larger sample sizes (n = 8104 and 4341 respectively vs n = 377), and different equations, but they also point to important differences in context. In the clinical decision making, education level and income may not be as relevant as they are for population health strategies.

Physical activity is another important consideration. Low cardiorespiratory fitness has been suggested as a predictor of MetS in a large cohort with BMI 22–25 kg/m^2 (LaMonte et al., 2005). Our data did not confirm this finding which may be due to the greater BMI of our clinical cohort. From a dietary perspective, dietary fatty acids of vegetable origin may have a beneficial effect on the incidence of MetS (Shab-Bidar et al., 2014). In our analyses no significant association was found between dietary fatty acids and MetS, however the sample size was possibly too small to detect these associations given variations in food choices.

Table 2
Baseline demographic and lifestyle covariates assessed in the multivariate logistic regression model of presence of MetS of Illawarra (NSW, Australia) participants.

Category	Baseline variable	Univariate analysis				Multivariate analysis			
		Coefficient	Lower 95% CI	Upper 95% CI	p	Odds	Lower 95% CI	Upper 95% CI	p
Demographic	Age	0.14	0.01	0.02	<0.01	1.08	1.04	1.12	<0.01
	BMI	0.05	0.04	0.06	<0.01	1.26	1.18	1.36	<0.01
	Gender	−0.12	−0.23	−0.01	0.03	0.55	0.30	1.02	0.06
	% body fat	0.01	0.01	0.02	<0.01	1.04	0.95	1.13	0.46
Psychological	DASS depression	0.01	−<0.01	0.02	0.19	1.03	0.96	1.10	0.43
	DASS anxiety	0.01	−0.01	0.03	0.21				
	DASS stress	<0.01	−0.01	0.02	0.57				
	DASS total	<0.01	−<0.01	0.01	0.23				
	SF-12 mental	<0.01	−<0.01	0.01	0.82				
Physical activity	IPAQ	<0.01	<0.01	<0.01	0.64				
	Steps/day S1[#]	−0.26	−0.48	−0.03	0.02	0.62	0.19	2.01	0.43
	Steps/day S2[#]	−0.27	−0.46	−0.07	0.01	0.61	0.22	1.66	0.33
	Steps/day S3[#]	−0.20	−0.37	−0.04	0.02	0.65	0.28	1.49	0.31
	Steps/day S4[#]	−0.25	−0.41	−0.10	<0.01	0.55	0.25	1.18	0.12
Dietary	Total kilojoules	<0.01	<0.01	<0.01	0.12	1.00	1.00	1.00	0.23
	MUFA	− < 0.01	−0.01	0.01	0.56				
	PUFA	− < 0.01	−0.02	0.01	0.46				
	Sat fat	<0.01	−<0.01	0.01	0.39				
Social	Household income C1[@]	−0.09	−0.24	0.06	0.24				
	Household income C2[@]	−0.02	−0.14	0.10	0.75				
	Education L1*	−0.25	−0.91	0.42	0.47				
	Education L2*	−0.20	−0.86	0.46	0.56				
	Education L3*	−0.10	−0.77	0.56	0.76				
	Education L4*	−0.05	−0.74	0.64	0.89				
	Education L5*	−0.22	−0.90	0.46	0.53				
	Education L6*	−0.05	−0.73	0.63	0.89				

Gender uses male as the referent category.[#]Steps/day S1 highly active, S2 active, S3 somewhat active, S4 low active. Steps per day are compared with sedentary as the referent category. [@] Household income category C1 >$160,000, C2 $80–$159,999. Household income compared with <$80,000 as the referent category. *Education L1 postgraduate degree, L2 university degree, L3 certificate/diploma, L4 trade/apprenticeship, L5 high school or leaving certificate, L6 school or intermediate certificate. Education levels are compared with no school certificate or other qualification as the referent category.

The main limitation of our sub-study is that MetS and lifestyle factors were secondary outcome measurements and the sample size was not specifically powered for addressing the relationships considered here. Likewise, the HealthTrack population was generally healthy and middle-aged albeit overweight, and this differed to other studies investigating younger or older populations. However from a public health and primary healthcare perspective it is most important to identify MetS in its earlier stages, that is, when people are healthy and before they develop CVD or insulin resistance. One other limitation was the use of medication, other than those included in the calculation of MetS, CVD, CHD and insulin resistance; they were not adjusted for in the multivariate analysis.

5. Conclusions

This study examined the utility of the harmonised equation for assessment of MetS in a clinical cohort of healthy overweight/obese volunteers and confirmed that those at greatest risk are older, overweight individuals. Once MetS is identified it is important to implement multi-disciplinary lifestyle changes due to the strong correlation with cardiovascular disease and insulin resistance. The classification of MetS will also be useful in determining the relative effects of lifestyle intervention over time.

Table 3
Estimated 10 year cardiovascular disease (CVD) risk and coronary heart disease (CHD) risk (n = 351) of Illawarra (NSW, Australia) participants.

Risk category	CVD[a]	CHD[b]
Low (<10%)	310 (88.3%)	324 (92.3%)
Moderate (10–20%)	39 (11.1%)	26 (7.4%)
High (>20%)	2 (0.6%)	1 (0.3%)

[a] Based on published equation (D'Agostino et al., 2008).
[b] Based on published score sheets (Wilson et al., 1998).

Conflicts of interest

Conflicts of interest: none.

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