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IS HAVING A FAMILY HISTORY OF TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE A PREDICTIVE FACTOR FOR METABOLIC SYNDROME?

Family history and metabolic syndrome

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ABSTRACT

Aims

To determine whether a first degree family history (FH) of diabetes and/or a first degree FH of cardiovascular disease (CVD), can predict prevalent cases of metabolic syndrome (MetS). Also, to establish if the association is different for South Asians compared to White Europeans, and for obese compared to non-obese individuals.

Methods

Cross-sectional data were analysed for a mixed-ethnic cohort of 3094 at-risk individuals, aged 40–75 years (29% South Asian), who were screened in Leicestershire (UK) for undiagnosed Type-2-diabetes using an oral glucose tolerance test. Logistic regression was used to assess the relationship between FH and prevalent MetS, including adjustment for potential confounders.

Results

Prevalence of MetS was 39%. Adjusted odds ratios (OR) showed that only a FH of CVD (OR 1.41, 95%CI: 1.18–1.68, p< 0.001) was significantly associated with prevalent MetS. Interaction analysis showed no effect modification for obesity and ethnicity. We did not find any association for a FH of diabetes.

Conclusions

These findings suggest that a first degree FH of CVD predicts prevalent cases of MetS in a mixed-ethnic population. Evidence of an association may help to identify individuals who should be targeted for screening and early prevention of Type-2-diabetes and CVD.

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KEYWORDS: METABOLIC SYNDROME; FAMILY HISTORY; DIABETES; CARDIOVASCULAR DISEASE.

INTRODUCTION

Metabolic syndrome (MetS) is characterised by a clustering of adverse risk factors for both cardiovascular disease (CVD) and type 2 diabetes (T2DM) Despite the lack of a consensus definition for MetS, the National Cholesterol Education Program (NCEP) [1,2] and the International Diabetes Federation (IDF) [3] definitions have in common impaired glucose metabolism, dyslipidaemia, hypertension, and central obesity. Both the NCEP and IDF definitions are aimed at being simple to use in the clinical setting, however, the NCEP definition has been the one most commonly used in previous epidemiological studies.

There is debate about the validity of MetS as a clinically useful concept and whether identifying MetS in patients adds anything over and above existing risk scores such as the Framingham CVD risk score [4]. However, evidence suggests that individuals with MetS are approximately twice as likely to have CVD (incident disease, event or mortality) [5] and 3 times as likely to develop diabetes [6] than people without MetS. Furthermore, MetS is of great importance to public health as it precedes T2DM and CVD by several years. Individuals with MetS could be an important group to target for early prevention of diabetes and CVD [7].

In the US, it is estimated that the age adjusted prevalence of MetS is 35% or 39% according to the NCEP and IDF definitions respectively [8]. Data for the UK are scarce but it is thought that up to 25% of the UK population have MetS [9] and this is likely to increase due to rising levels of obesity and more sedentary lifestyles. Additionally, the prevalence of MetS increases with age [8], is higher in certain ethnic groups such as South Asians (SAs) and Afro-Carribeans [10], and is higher in socio-economically disadvantaged groups [11,12,13].

Both genetics and environmental factors play a role in the development of MetS [14,15] and the chromosomal regions thought to be involved have previously been linked to an increased risk of CVD and T2DM [14]. Body mass index (BMI) is commonly included in studies and may be considered to be a good proxy measure for environmental factors because of its association with lifestyle habits (physical activity and diet). In the absence of formal genetic testing, family history

(FH) is often seen as a good proxy measure for specific genetic susceptibility [16, 17].

For many chronic diseases it is widely accepted that a positive FH is a risk factor [18]. There is some evidence that an association exists between a positive FH of diabetes and/or a FH of CVD and prevalent MetS but previous data are limited [12,19-23]. There is a lack of information from UK populations in general and specifically comparing SAs with other ethnic groups, despite an increased risk and younger age of presentation of diabetes and CVD in SAs [24]. The objectives of this study were to determine whether a first degree FH of diabetes and/or first degree FH of CVD, or the number of relatives with diabetes, can predict prevalent cases of MetS, and to determine if the association is different for SAs compared to WEs, and obese compared to non-obese individuals. Evidence of an association could be useful for targeting screening/prevention programmes.

METHODS

Study population

For our analyses we used cross-sectional data collected for the Screening Those At Risk (STAR) study [25]. STAR is part of the Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) study, a large screening study involving a multi-ethnic population from Leicestershire, UK. The STAR study recruited people from 15 general practices and aimed to detect undiagnosed T2DM using a 75g oral glucose tolerance test (OGTT). Individuals invited for screening had at least one risk factor for T2DM, including first degree FH of diabetes, coronary heart disease (CHD), hypertension, stroke, overweight, and hyperlipidaemia. Additional baseline measures collected included demographic details, bio-chemical and anthropometric measures, significant medical history (past and current), and family medical history of diabetes and CVD.

MetS was defined using the original NCEP definition [1], but also including prescribed medication for dyslipidaemia and hypertension. Other important study variables were defined according to the criteria in Table 1.

Statistical analysis

Independent-sample t-tests or chi-square tests were used to compare between group differences for people identified as having prevalent MetS and those without. Logistic regression modelling was carried out to investigate whether a first degree FH of DM and/or CVD was associated with increased odds for prevalent MetS and whether the number of first degree relatives with diabetes was associated with prevalent MetS. Odds ratios (ORs) were adjusted for the following potential confounders: obesity, ethnicity, gender, age, smoking, and Indices of Multiple Deprivation scores (IMD-scores) [26]. Additionally, interaction terms for FH and obesity and for FH and ethnicity were added to the models to determine whether the associations were different for SAs compared to WEs, and for obese compared to non-obese individuals.

Further analyses were carried out to evaluate any model that showed a significant association between the FH variable of interest and prevalent MetS. The Hosmer and Lemershow test statistic was used as an indicator of goodness of fit. The multivariable correlation matrix (produced in SPSS) of the estimated

correlations between the variables in the model was inspected for multi-collinearity. Additional modelling (effect modification) was carried out to determine whether the associations found varied according to gender, smoking, IMD-score or age, by adding interaction terms to the models. Statistical significance was assessed at the 5% level and 95% confidence intervals were calculated for all the main results, and all tests were two-sided. Statistical Package for the Social Sciences (SPSS) version 16.0 was used for all data analyses.

RESULTS

Sample characteristics

We analysed data for 3094 individuals aged 40 – 75 years (WEs and SAs) for whom sufficient screening information was available to classify MetS status. The characteristics of the population, overall and by prevalent MetS status, are outlined in Table 2. Overall, the mean age was 57 years, 46% were male, 29% were of SA ethnicity, and mean BMI was 28 kg/m^2. Results of the OGTT classified 6% of people as having T2DM, and 16% as having either impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both. Self-reported family medical histories (first degree) were 39%, 46% and 18% respectively for diabetes, CVD or both; 28% of individuals reported one relative with diabetes and 11% reported $\geq$ 2 relatives.

The overall prevalence of MetS was 39% but showed significant differences according to ethnicity and gender, (Table 3). A higher proportion of males (42%) had MetS compared to females (36%), p=0.001, and more WEs (40%) had MetS compared to SAs (35%), p=0.006. However, when gender differences were compared within ethnic groups, the prevalence remained higher for WE males (45%) compared to WE females (37%), p<0.001, but for SAs there was no significant gender difference.

There were significant differences between individuals with MetS and those without with respect to most variables related both to risk factors and clinical outcomes, (Table 2). Compared to individuals without MetS, those with MetS were significantly older (59 vs. 55 years), had higher IMD-scores (27 vs. 25), and were more likely to have a medical history of CVD or hypertension, or have some degree of impaired glucose metabolism at screening. However, total and LDL (low density lipoprotein) cholesterol were both significantly higher in individuals without MetS than those with MetS; 5.5 vs. 5.3 mmol/l, and 3.5 vs. 3.3 mmol/l respectively for total and LDL cholesterol. Although a much higher proportion of people with MetS compared to people without reported taking cholesterol lowering medication, statins or fibrates, (33% vs. 1%). A significantly lower proportion of those with MetS were current smokers (22% vs. 26%).

Modelling

Unadjusted ORs indicated that only a first degree FH of CVD was significantly associated with an increased likelihood of having MetS (OR=1.26, 95%CI: 1.09–1.47, p=0.002). A first degree FH of diabetes, first degree FH of both diabetes and CVD and the number of first degree relatives with diabetes showed no significant associations. After all models were adjusted for potential confounders, a first degree FH of CVD remained the only variable associated with prevalent MetS, with an increased odds ratio of 1.41 (95%CI: 1.18–1.68, p<0.001) (Table 4).

Interaction analyses carried out to examine whether the associations between the various FH variables and MetS were the same for obese and non-obese individuals, and for individuals who were of WE and SA ethnicity, showed no significant interactions.

Statistical evaluation of the first degree FH of CVD model provided no evidence that the model was a poor fit to the data (Hosmer and Lemeshow test, p=0.437). Additional support for the model was demonstrated by a lack of multi-collinearity (correlations all <0.4). Furthermore, no significant effect modification was demonstrated when interaction terms for FH and gender, FH and IMD-score, and FH and smoking were added to the model. The interaction term for FH of CVD and age was significant (OR=1.02, 95%CI: 1.00–1.04, p=0.026) but due to the number of tests performed, using the Bonferroni correction, this may reasonably be assumed to be just a chance occurrence.

DISCUSSION

Results from the analysis of cross sectional data suggest that a first degree FH of CVD is associated with increased likelihood of having MetS in a mixed ethnic-population, after adjusting for age, gender, ethnicity, obesity, deprivation, and smoking status. Interaction analyses showed no evidence that the effects of a positive FH of CVD on the prevalence of MetS differed between individuals who were obese or non-obese, or between SAs and WEs. In our sample, there was no evidence of an association between MetS and a first degree FH of diabetes, a FH of one or ≥two first degree relatives with diabetes (compared to no relatives), or a FH of both diabetes and CVD combined.

This study has a number of strengths. The large sample size increased the ability of the study to detect clinically important effects, and the relatively small proportion of individuals with missing data for variables (96% complete data for all variables except IMD-score where 86% were available), lessened the possibility of the results being seriously affected by item-non-response bias. Additionally, rigorous study protocols adopted for the STAR study, including the use of standard operating procedures maximised the accuracy of the data collected. Furthermore, multi-variable modelling enabled adjustments to be made for multiple confounders known to be associated both with MetS and with the explanatory variables of interest (FH variables). The precision of our results is indicated by the small widths of the 95% confidence-intervals for all ORs.

We acknowledge that our study may have limitations associated with conducting secondary data-analysis. For example, the STAR study aimed to detect undiagnosed T2DM, so individuals who might have a FH of diabetes but who were already diagnosed as having T2DM were excluded. This may have introduced bias within our sample as it is likely that a large proportion of those with existing diabetes would have met the criteria for MetS.

A further limitation is the possibility of inaccuracies in the FH data due to recall-bias or lack of understanding or knowledge. However, there is no reason to believe that recall-bias would affect subjects with or without MetS differently. It is

also acknowledged that there are likely to be limitations in terms of using BMI and FH as proxy measures in place of detailed information relating to lifestyle and genetic risk factors. Additionally, we were not able to consider the specific relationship of first degree relatives, (mother, father, or sibling), or the age at which diabetes or CVD was diagnosed. There is some evidence from previous studies that maternal FH is more strongly associated with components of MetS than paternal FH [27,28], and that early age of onset of FH of diabetes increases the association between FH and MetS [29].

There may be limitations associated with the NCEP definition of MetS used in this study. This definition includes a criterion for waist circumference but this is not ethnic-specific, despite an increased risk for a smaller measurement in some groups such as SAs [30]. The newer IDF definition [3] takes into account ethnic-specific values for waist circumference. However, the majority of outcome data for MetS are currently from studies using the original NCEP definition and use of this definition for our study facilitated comparison of findings.

Overall prevalence of MetS in this study (39%) is similar to age adjusted estimates for the US (35% NCEP, 39% IDF) [8]. However, compared to a previous UK study [10] ethnic specific prevalence in our study differed. The previous UK study found that the age adjusted prevalence of MetS (NCEP definition [3]) was higher for SAs (29% males, 32% females) compared to WEs (18% males, 14% females). In contrast, our study suggests a higher prevalence in WEs compared to SAs for both genders (WEs: males 45%, females 37%; SAs: males 35%, females 35%).

The lack of an association between a FH of diabetes and prevalent MetS found in our study is in contrast to a small number of previous studies [19-22] that reported odds ratios for MetS of between approximately 1.5 and 3 for people with a positive FH of diabetes compared to those without a FH. However, none of the studies specified a first degree FH. Additionally, in 2 of the studies all participants had existing coronary artery disease [21] or T2DM [22], and neither of these studies adjusted for potential confounders. The mean age of the populations of the remaining 2 studies, conducted in Hong Kong Chinese men [19] and in

Venezuela [20], at 39 and 44 years respectively, was much younger than for our study. However, a study conducted prior to the publication of any formal definitions for MetS, but including relevant criteria, reported a similar finding to our own, namely that a first degree FH of diabetes did not predict prevalent MetS.

The association we found between a FH of CVD and MetS shows similarities with 2 previous studies conducted in Korea [12] and the US [23], which used the NCEP definition [3] of MetS. One of these studies reported an association between FH of CVD and prevalent MetS (RR 1.5) [12] and the other found that the prevalence of MetS was significantly higher in people with a FH of CAD than without after adjusting for age, gender and race (21% versus 13% respectively, $p<0.01$) [23]. A UK study [32] that considered FH of a stroke demonstrated limited associations with some of the individual components of MetS.

To our knowledge, no previously published studies that considered FH and MetS have specifically compared SAs to WEs. In our study no ethnic differences were found for associations between prevalent MetS and FH of diabetes and/or CVD when interaction analyses were carried out. However, this study provides evidence that a FH of CVD is significantly associated with an increased likelihood of having MetS in a mixed-ethnic population of people without a previous diagnosis of T2DM. Effect modification indicated that increased odds persist regardless of whether an individual is obese or non-obese, male or female, a current smoker or non-smoker, and regardless of IMD score.

The ability to identify patients with MetS in primary care, in order to intervene early and reduce future health risk, is potentially of great importance to public health. Individuals with MetS are at increased risk of developing both CVD and diabetes and MetS can precede both diseases by several years. This study provides evidence to suggest that individuals in at risk populations who have a first degree FH of CVD should be targeted and screened for MetS and also highlights the importance of routinely recording FH in medical records. In primary care all patients aged 40 and above who have a first degree FH of CVD could be offered screening for MetS. Patients identified as having MetS could

subsequently be offered lifestyle advice, and where appropriate pharmacological therapy, according to current guidance [2-4,33].

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MJD and KK were principal investigators of the STAR study. All authors contributed to the drafting and revision of the manuscript and approved the final version submitted for publication.

Declarations:

Ethical approval: The STAR study was conducted in accordance with the approval granted by the Leicestershire, Northamptonshire and Rutland NHS research ethics committee. Informed consent was gained from volunteers prior to their participation. This study forms part of the wider analysis of the STAR study data.

Conflict of interest: KK and MJD have received sponsorship for attending conferences and honorariums from pharmaceutical companies that manufacture drugs for hyperglycaemia and anti-obesity drugs. AJD has received sponsorship for attending conferences.

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