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Familial components of the multiple metabolic syndrome: the ARIC Study

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Summary The association of a parental history of diabetes mellitus and hypertension with the multiple metabolic syndrome (MMS) was studied in a population survey of middle-aged adults. The eligible population was drawn from the baseline examination of the Atherosclerosis Risk in Communities Study, a population-based, bi-ethnic, multi-centre cohort study. The MMS was defined as a multivariate, categorical phenotype of co-occurring diabetes, hypertension, and dyslipidaemia. MMS cases (n = 356) were compared to disorder-free control subjects (n = 6797) with respect to their parental history of diabetes and hypertension. MMS cases were more likely to report a history of diabetes in both parents (odds ratio [OR] 4.7, 95% confidence interval (CI) 1.5–14.7) or a history of hypertension in both parents (OR 1.9, 95% CI 1.1–3.0) than control subjects, adjusting for BMI, waist-to-hip ratio, age, gender, and ethnicity/centre. A parental history of diabetes and hypertension in both parents was associated with the greatest increase in odds of MMS (OR 8.3, 95% CI 3.0–22.8). A dose-response relationship between the number of parental disorders (one; two; three to four) and the odds of MMS was observed (OR 1.2, 95% CI 0.9–1.7; OR 2.0, 95% CI 1.4–2.8; OR 4.0, 95% CI 2.5–6.2). Based on the marked associations observed between a parental history of MMS components and the clustering of these metabolic disorders in the offspring generation, we conclude that genetic and/or non-genetic familial influences play a role in the development of the multiple metabolic syndrome. [Diabetologia (1997) 40: 963–970]

Keywords Parental history, insulin resistance syndrome, non-insulin-dependent diabetes mellitus, hypertension.

The clustering of multiple metabolic abnormalities including obesity, insulin resistance, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, and dyslipidaemias has become known as the insulin resistance syndrome [1, 2] or multiple metabolic syndrome (MMS) [3, 4]. Genetic as well as shared environmental influences on insulin, insulin resistance, and obesity have been reported in family and twin studies [5–11]. Familial aggregation of NIDDM [12, 13], elevated blood pressure levels [14, 15], and lipid disorders [16, 17] is well established. Metabolic disorders such as familial hypercholesterolaemia [18, 19], familial combined hyperlipidaemia [20–22], and familial dyslipidemic hypertension [23] require a positive family history as part of their definition.

Particularly within genetic epidemiology, studies on the MMS have frequently had a primary focus on a single, continuously distributed metabolic characteristic such as insulin [8, 9]. Others have compared multiple metabolic variables among offspring of affected and unaffected parents [24–31]. Focusing on a single metabolic characteristic, however, limits the

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Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; MMS, multiple metabolic syndrome; NIDDM, non-insulin-dependent diabetes mellitus; OR, odds ratio; PHxSum, parental history summary score; WHR, waist-to-hip ratio.

ability to study a defining aspect of the MMS, its clustering characteristics. To date, multivariate approaches to the MMS have only been demonstrated in a number of twin [32–35] and family studies [36]. These studies have pointed towards strong genetic or shared environmental influences on the joint occurrence of MMS components [32, 33]. Recently, Mitchell et al. [36] suggested that a common gene or set of genes may influence components of the MMS such as insulin, BMI, triglycerides, and HDL-cholesterol.

To our knowledge, few population-based studies have addressed familial components of the MMS, particularly using a multivariate phenotype definition of the MMS [37]. We therefore defined the MMS as co-occurring diabetes, hypertension, and dyslipidaemias. The purpose of our study was to elucidate the cross-sectional association of a parental history of diabetes and hypertension with the MMS. We hypothesized that both a parental history of diabetes and a parental history of hypertension would be associated with the MMS. Additionally, a larger number of positive parental histories was expected to be associated with increasing odds of MMS.

Subjects and methods

Study population. The study population was drawn from the baseline examination (1987–1989) of the Atherosclerosis Risk in Communities (ARIC) Study, a bi-ethnic, population-based cohort study of the natural history and aetiology of atherosclerotic disease conducted in four United States communities. Study participants were identified by probability sampling in Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. Details of the study design have been described previously [38, 39]. The study was conducted after approval by the United States Office of Management and Business and after review by the institutional review boards for research on human subjects. All participants gave written informed consent prior to inclusion in the study. Of the 15792 ARIC participants, we excluded 592 individuals who had been fasting less than 8 h prior to venipuncture, 51 individuals outside the 45–65 year age range, 98 participants of other ethnic minorities, and 645 individuals missing data. Our final study population comprised 14406 individuals: 3523 African-Americans and 10883 European-Americans.

Data collection. Information on the parental history of diabetes and hypertension was collected in a structured home interview during enrollment. Participants were asked "Did your natural mother (father) ever have (or does she (he) have now) any of the following diseases?" and could answer "yes", "no", and "unsure" for the diseases diabetes (sugar in the blood) and high blood pressure (hypertension, high blood). Individuals with truly missing information were excluded. We chose not to exclude anyone with an "unsure" response (approximately 25%) because of potential selection bias. Instead, "unsure" answers were coded as a negative parental history since the ensuing misclassification would result in a conservative bias.

All participants underwent an extensive, standardized medical examination and interview. Fasting serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Total triglyceride and HDL-cholesterol levels were measured by enzymatic methods, dextran-magnesium precipitation being used for HDL-cholesterol. Sitting systolic and diastolic blood pressure was measured three times after a 5-min rest using a random zero sphygmomanometer and the last two measurements were averaged. Participants were dressed in scrub suits and not wearing shoes during anthropometric measurements (height, weight, abdominal girth, hip circumference). BMI (kg/m^2) and waist-to-hip ratio (WHR) were derived. Trained interviewers ascertained information on medical history and medication use [40].

Study design. From the family history questionnaire, two types of parental history variables were derived. The parental history summary score (PHxSum) added the *number* of disorders (diabetes and hypertension) among both parents and ranged from zero to four. The second parental history variable assessed both the *number* and *type* of parental disorders, but ignored the gender of the affected parent. Since each parent can be unaffected, diabetic, hypertensive, or both diabetic and hypertensive, 16 distinct combinations are possible. They collapse into nine combinations if – as in our study – the gender of the parent is not considered. Parental history variables were included as design variables in all statistical models.

Diabetes, hypertension, and dyslipidaemias were considered components of the MMS. Diabetes was defined as being on hypoglycaemic medication as verified at the clinic visit and/or exhibiting a fasting glucose level greater than 7.8 mmol/l (140 mg/dl) using the cutoff points of the World Health Organization criteria [41]. Hypertension was defined as having a systolic blood pressure greater than 140 and/or diastolic pressure greater than 90 mm Hg and/or being on antihypertensive medication [42]. Dyslipidaemias were defined as having fasting triglycerides greater than 2.26 mmol/l (200 mg/dl) and/or HDL-cholesterol less than 35 mg/dl (0.9 mmol/l) for men [43]. For women, a higher cutpoint was used (HDL cholesterol less than 1.2 mmol/l (45 mg/dl). Lipid lowering medication was not part of the dyslipidaemia definition because indication of use was not ascertained. Misclassification of dyslipidaemia should be minimal in this respect because Nieto et al. [44] have shown that only 4% of hypercholesterolaemic ARIC participants were medically well controlled. MMS cases were defined as having the three clinical disorders: diabetes, hypertension, and dyslipidaemia simultaneously.

Statistical analysis. The distribution of the MMS components was tabulated and its clustering characteristics evaluated: Observed to expected ratios (O/E) were calculated under the assumption of independence separately for each ethnic/gender group. The expected were calculated by multiplying the overall prevalence of each component disorder with the term(s) 1 minus the prevalence of that (those) disorder(s) not part of the cluster [45, 46]. An example is provided in the results. Multiple logistic regression was used to model the hypothesized association between the parental history variables and the MMS, derive odds ratios (OR) and 95% confidence intervals (95% CI). Effect-modification by ethnicity, gender, and obesity was evaluated. Unless otherwise indicated, effect estimates were adjusted for age, gender, ethnicity, centre, BMI, and WHR. MMS cases ($n = 356$) were contrasted with disorder free control subjects ($n = 6797$) with respect to their parental history. To address the question whether MMS cases have an excess risk of a parental history, MMS cases were compared firstly to all others with diabetes ($n = 663$) in the study population (those with isolated diabetes and pairs of abnormalities that include diabetes) and secondly to all others with hypertension

Table 1. Multiple metabolic disorder status of the ARIC study population (1987–1989) by ethnicity and gender

MMS component disorders	Total population			African-American						European American					
	(n = 14406)			Women (n = 2189)			Men (n = 1334)			Women (n = 5767)			Men (n = 5116)		
	%	n	O/E[c]	%	n	O/E[c]	%	n	O/E[c]	%	n	O/E[c]	%	n	O/E[c]
Disorder-free[a]	47.2	6797	1.10[d]	33.4	731	1.12[d]	35.7	476	1.10[f]	54.9	3165	1.10[d]	47.4	2425	1.10[d]
Diabetes	1.2	171	0.36[d]	2.0	43	0.46[d]	2.9	39	0.70[f]	0.6	37	0.25[d]	1.0	52	0.38[d]
Hypertension	20.0	2879	0.90[d]	35.8	783	0.97	36.8	491	0.97	14.8	851	0.83[d]	14.7	754	0.86[d]
Dyslipidaemia	16.1	2314	0.88[d]	7.9	173	0.86[f]	6.1	81	0.74[e]	16.6	959	0.83[d]	21.5	1101	0.89[d]
Diabetes + hypertension	1.9	277	1.14[f]	5.2	114	0.98	4.5	60	0.90	0.9	50	0.92	1.0	53	0.97
Diabetes + dyslipidaemia	1.5	215	1.08	1.5	32	1.09	1.3	18	1.26	1.4	81	1.33[e]	1.6	84	1.10
Hypertension + dyslipidaemia	9.7	1397	1.03	10.3	225	0.90	9.8	131	1.03	8.7	504	1.21[d]	10.5	537	1.10[f]
MMS[b]	2.5	356	3.45[d]	4.0	88	2.43[d]	2.8	38	2.26[d]	2.1	120	5.46[d]	2.2	110	3.62[d]

[a] Disorder-free is defined as non-diabetic, non-hypertensive, and non-dyslipidaemic;
[b] Co-occurring diabetes, hypertension, and dyslipidaemia;
[c] Observed-to-expected ratios calculated under assumption of independence of diabetes, hypertension, and dyslipidaemia, separately by gender/ethnic group;
[d] $p < 0.005$;
[e] $p < 0.01$;
[f] $p < 0.05$ from Chi-Square test of independence

Table 2. Characteristics of multiple metabolic syndrome cases and disorder-free control subjects in the ARIC study population (1987–1989)

Variables	MMS cases (n = 356)	Disorder-free control subjects (n = 6797)
Age (years)	56.8 ± 5.3	53.5 ± 5.7
African-American (%)	35.2 ± 2.5	17.8 ± 0.5
Female (%)	58.6 ± 2.6	57.3 ± 0.6
Body mass index (kg/m^2)	32.3 ± 5.7	26.0 ± 4.5
Waist-to-hip ratio	0.99 ± 0.06	0.90 ± 0.08
0 Parental disorders (%)	27.5 ± 2.4	40.8 ± 0.6
1 Parental disorder (%)	35.1 ± 2.5	38.8 ± 0.5
2 Parental disorders (%)	25.3 ± 2.3	16.4 ± 0.5
3–4 Parental disorders (%)	12.1 ± 1.7	4.0 ± 0.2

Data are mean ± SD

(n = 4553). All statistical analyses were performed with the SAS statistical package (version 6.11).

Results

The distribution of the MMS component disorders diabetes, hypertension, and dyslipidaemias in the study population is depicted by gender and ethnicity in Table 1. Half of the European-American population was free of MMS component disorders compared to 34% of the African-American population. Both diabetes and hypertension occurring in isolation were substantially and significantly more prevalent in African-Americans, while dyslipidaemias were more prevalent in European Americans. Ethnic differences were less pronounced for pairs of metabolic disorders with the exception of diabetes plus hypertension, which was more prevalent in African-Americans. The highest prevalence of the MMS (having all three disorders) was evident in African-American women (4%). Observed to expected (O/E) ratios assessed the clustering of MMS components beyond chance. For example, we observed the overall frequencies of 7.07% for diabetes, 34.08% for hypertension, and 29.72% for dyslipidaemias in the total population (n = 14406). The expected number of cases of concurrent diabetes and hypertension was calculated as $[0.0707 \times 0.3408 \times (1 - 0.2972)] \times 14406 = 244$. Since 277 cases were observed, the O/E ratio is 1.14 which may be interpreted as a 14% excess co-occurrence of diabetes and hypertension beyond that expected due to chance. Overall, the O/E ratios indicated an excess of individuals free of MMS component disorders and an excess of individuals with clusters of three disorders. A statistically significant deficit of isolated disorders (for example isolated diabetes O/E = 0.36) was observed.

Characteristics of MMS cases and disorder-free control subjects are shown in Table 2. MMS cases tended to be older, more obese, exhibit a more central pattern of fat deposition than disorder-free control subjects, and were more likely to have multiple parental histories. Additionally, a smaller proportion of the cases' mothers and fathers were alive at the time of the interview (data not shown). The proportion of African-Americans and women was higher among cases than among control subjects.

The association of parental histories of diabetes and hypertension with the MMS is depicted in Table 3. The odds ratios for each of the mutually exclusive parental history combinations are derived from one model containing eight design variables. Compared to disorder-free individuals, MMS cases were slightly more likely to have only an isolated parental history of diabetes (OR 1.31, 95% CI 0.84–2.04) or an isolated parental history of hypertension (OR 1.22, 95% CI 0.88–1.68) adjusted for age, gender, ethnicity/centre, BMI, and WHR. Any combination of two or more parental disorders was associated with a substantially increased odds of being an MMS case. A parental history of diabetes and hypertension in

Table 3. Association of the multiple metabolic syndrome (MMS) with various parental history combinations, contrasting MMS cases with disorder-free control subjects

Number and type of parental history disorders	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
None	1.00	1.00
1 × DIAB	1.54 (1.01–2.33)	1.31 (0.84–2.04)
1 × HTN	1.42 (1.06–1.91)	1.22 (0.88–1.68)
1 × DIAB and 1 × HTN	2.48 (1.74–3.53)	1.96 (1.33–2.91)
2 × DIAB	3.83 (1.30–11.26)	4.66 (1.48–14.68)
2 × HTN	2.28 (1.48–3.50)	1.85 (1.14–3.03)
2 × DIAB and 1 × HTN	6.36 (2.81–14.36)	4.38 (1.68–11.44)
2 × HTN and 1 × DIAB	4.45 (2.82–7.01)	3.41 (2.04–5.68)
2 × DIAB and 2 × HTN	7.13 (2.66–19.12)	8.26 (2.99–22.80)

DIAB, Diabetes; HTN, hypertension
[a] Adjusted for age, gender, ethnicity/centre;
[b] Adjusted for age, gender, ethnicity/centre, body mass index, waist-to-hip ratio

both parents, however, was associated with the greatest increase in odds of MMS (OR 8.26, 95% CI 2.99–22.80). As expected, BMI and WHR were significantly and independently associated with both the MMS and the parental histories. Adjusting for these correlates did not influence the parental history – MMS association substantially.

The association between the number of parental histories as expressed in the parental history summary score (PHxSum) and the MMS is shown in Table 4 (first column). As observed above, MMS cases were slightly more likely than disorder-free control subjects to have a single parental history (of either diabetes or hypertension) (OR 1.24, 95% CI 0.92–1.67) adjusted for age, gender, ethnicity/centre, BMI, and WHR. However, MMS cases were significantly more likely to have a PHxSum of two (OR 1.99, 95% CI 1.42–2.79) and substantially more likely to have a PHxSum of three to four (OR 3.96, 95% CI 2.54–6.17) than disorder-free control subjects (test for linear trend p-value < 0.0001). Ethnicity, gender, or obesity did not modify these effects. Very similar trends of increased odds of MMS with increasing number of parental disorders (one; two; three to four) were observed among the two ethnic groups after stratification. The odds ratios (and 95% CI) were in that order 0.66 (0.39–1.12); 1.78 (1.04–3.06); 4.06 (1.99–8.28) in African-Americans and 1.68 (1.17–2.43); 1.95 (1.26–3.03); 3.83 (2.14–6.85) in European-Americans.

We were furthermore interested in the question whether MMS cases have an excess risk of a parental history of diabetes and hypertension. Table 4 (second column) shows the results of comparing MMS cases to all others with diabetes in the study population, i.e. those that have diabetes in isolated form or in combination with any one additional disorder. Our results indicate that MMS cases were not different from all others with diabetes with regard to having an isolated parental history or two disorders among the parents controlling for age, gender, ethnicity/centre, BMI, and WHR. However, they were more likely to have three or more MMS component disorders in their parental generation (OR 1.69, 95% CI 1.03–2.77). Secondly, in comparison to all others with hypertension (Table 4, third column), MMS cases basically had the same likelihood of having one parental history. They were, however, substantially more likely to have a PHxSum of two (OR 1.41, 95% CI 1.03–1.92) or three to four (OR 2.55, 95% CI 1.70–3.83). Additional analyses focused on the *type* of parental history that contributed to the observed association. MMS cases differed from all others with diabetes primarily with respect to their excess parental history of hypertension. Conversely, compared to all others with hypertension MMS cases more frequently exhibited a parental history of diabetes (data not shown).

Table 5 depicts the results focusing first exclusively on a parental history of diabetes and subsequently on a parental history of hypertension with regard to differences in a maternal compared to a paternal history. MMS cases were compared to disorder-free control subjects. Again, MMS cases were more than four times as likely to have two diabetic parents than disorder-free control subjects. A maternal-only history of diabetes was associated with a slightly stronger odds of being an MMS case than a paternal-only history, but the odds ratios did not differ much and the confidence intervals clearly overlapped. A similar picture emerged for a maternal compared to a paternal history of hypertension. However, a paternal-only history of hypertension was not associated with the MMS.

Table 4. Association of the multiple metabolic syndrome (MMS) with the number of parental histories

Exposure	Case-Control contrasts		
Number of parental histories (PHxSum)	MMS vs disorder-free control subjects (n = 356 : 6797) OR (95% CI)[a]	MMS vs all others with diabetes (n = 356 : 663) OR (95% CI)[a]	MMS vs all others with hypertension (n = 356 : 4553) OR (95% CI)[a]
0	1.00	1.00	1.00
1	1.24 (0.92–1.67)	0.89 (0.64–1.25)	0.99 (0.75–1.31)
2	1.99 (1.42–2.79)	1.12 (0.78–1.62)	1.41 (1.03–1.92)
3–4	3.96 (2.54–6.17)	1.69 (1.03–2.77)	2.55 (1.70–3.83)

[a] Adjusted for age, gender, ethnicity/centre, body mass index, waist-to-hip ratio

Table 5. Association of the multiple metabolic syndrome (MMS) with a parental history of diabetes and hypertension, differentiating by gender of the affected parent

	Parental history of diabetes OR (95% CI)[a]	Parental history of hypertension OR (95% CI)[a]
Neither parent affected	1.0%	1.0%
Mother only	1.67 (1.24–2.25)	1.40 (1.06–1.86)
Father only	1.57 (1.03–2.39)	1.14 (0.73–1.78)
Both parents affected	4.65 (2.54–8.50)	2.39 (1.67–3.41)

[a] Contrasting MMS cases with disorder-free control subjects and adjusted for age, gender, ethnicity/centre, body mass index, waist-to-hip ratio

Discussion

The major limitation of our study is that the parental history information is based on the participants' report. Validation data [47] from the Family Heart Study (which comprises part of the ARIC population) reveal that the accuracy of a reported family history of diabetes (sensitivity 73%, specificity 98%) is substantially higher than that of hypertension (58%, 92%) which implies more misclassification of hypertension than diabetes. A particular concern would be differential recall by MMS status, i.e. recall bias. The only validation data found in the literature which differentiated by case and control status focused on coronary heart disease (CHD) [48] and basically found no major differences in the recall accuracy of a family history of diabetes by affected status but a higher sensitivity of reporting a family history of hypertension among cases of CHD. By assigning anyone expressing uncertainty about their parental history to the group with a negative parental history, additional inaccuracies were introduced. As expected, repeating the analyses excluding anyone answering "unsure" resulted in stronger estimates of association, although statistical power was reduced due to the reduced sample size. Finally, undiagnosed diabetes and hypertension in the parental generation may well have been an additional source of misclassification. In this context, we speculate that the observed association of a parental history of hypertension may in fact be an underestimate. While we cannot exclude the possibility that misclassification and bias have affected the results for a parental history of diabetes, it seems unlikely that they are entirely responsible for the strong associations observed in our data.

A number of methodological studies have addressed the validity of the use of family histories in case-control studies [49–51], since a family history is not only the attribute of a person but depends on the number of relatives, their age distribution and age at diagnosis, vital status and more [49]. Since we focused on a parental history instead of a family history, bias related to the number of relatives considered should be minimal [49]. Additionally, our study is nested within a cross-sectional population study and thus less likely to be influenced by ascertainment bias. While an excess maternal transmission of NIDDM has been suggested by several studies based on self-report by the proband [13, 52], Mitchell et al. [53] could not confirm this finding in a study which tested both parents and offspring for diabetes. They concluded that reporting bias may be partly responsible for some of the previous findings. Our results are consistent with this conclusion, since the magnitude of the association of a maternal history of diabetes (or hypertension) with the MMS was very similar to a paternal history of diabetes (or hypertension).

While many metabolic impairments have been proposed as components of the MMS [1, 2, 4, 54–57], to our knowledge no suggestions have been offered on which of these disorders, or how many of them, are needed to diagnose a metabolic syndrome. We chose the disorders diabetes, hypertension, hypertriglyceridaemia, and low HDL cholesterol for their consistency with the concept of the MMS and their clinical relevance. Our study was thus based on a multivariate, categorical MMS definition. Carmelli et al. [33] used a similar categorical and multivariate definition of the MMS; namely diabetes, hypertension, and obesity in a study of male twins. The proband concordance for a cluster of all three disorders was significantly higher in monozygotic (31.6%) than in dizygotic (6.3%) twins (corresponding to a relative risk of 5.0). These results suggests the presence of an underlying genetic factor and are consistent with those reported by Selby et al. [32] for dyslipidemic hypertension. Our study indicates that both a parental history of diabetes and hypertension are strongly and statistically significantly associated with the MMS as defined by co-occurring prevalent diabetes, hypertension, and dyslipidaemia. The advantage of using a multivariate and categorical MMS definition is that a risk quantification via odds ratios is possible. The magnitude of the associations was noteworthy, as the various parental history combinations were associated with an increase in odds of having MMS ranging from 1.2 to 8.3. We furthermore observed a dose-response-like relationship between the number of parental disorders and the odds of MMS.

Carmelli et al. [33] additionally employed multivariate genetic modelling and their results suggest the influence of a common latent factor mediating the clustering phenomenon. This factor was influenced both by environmental as well as genetic factors. Mitchell et al.'s findings [36] are consistent with this concept of a common gene or set of genes (pleiotropy). They found high genetic correlations between insulin and BMI, HDL cholesterol, WHR, and subscapular-to-triceps ratio. Recently, Hong et al. [35] reported that insulin resistance, BMI, triglycerides, HDL-cholesterol and systolic blood pressure were

all influenced to some degree by a common latent genetic factor. These and other findings [27] provided the rationale for the concept of studying the joint contribution of a parental history of diabetes and hypertension. Our results indicate that a parental history of diabetes may confer a higher degree of risk of MMS than a parental history of hypertension both individually and as part of a cluster of parental histories. This result should be interpreted with caution given the limitations related to self-report but is consistent with results of Wing et al. [29] and the genetic importance of insulin resistance and obesity in MMS development [35].

Focusing on the potential interaction of a parental history of diabetes and hypertension, we evaluated our results both on an additive and a multiplicative scale. The former provided the basis for our conclusions as it has been suggested as appropriate for an epidemiologic and public health context [58]. The risk differences observed between various parental history combinations point towards a greater than additive effect of their joint presence on the odds of MMS. For example, the OR of having the MMS given two parents with diabetes was 4.66 and the respective OR for two parents with hypertension was 1.85. Therefore, the expected joint effect of having both parents affected with both disorders is estimated as OR = (4.66 –1) + (1.85 –1) = 4.51. As the observed OR is 8.26 and exceeds the expected, we conclude that a greater than additive effect of these particular parental history combinations is consistent with our data.

To address the question of excess familial predisposition on a conceptual level, we compared the parental histories of individuals with the MMS to those who already exhibited one or two MMS component disorders (either all others with diabetes or all others with hypertension). Since these groups would be expected to exhibit a higher frequency of parental histories themselves, any remaining significant associations between the MMS and the parental history summary score (PHxSum) might be interpreted as indicative of excess risk of familial clustering. Our results show that MMS cases were indeed significantly more likely to have three to four MMS component disorders among their parents than all other diabetic subjects. They were also significantly more likely to have two or three to four disorders among their parents than all other hypertensive subjects. Thus, at least some of the observed association of the parental histories with the MMS is not explained by the expected higher prevalence of a parental history of diabetes (or hypertension) in diabetic and hypertensive MMS cases.

In summary, our data demonstrated a strong association between a parental history of MMS components and the clustering of these metabolic disorders in the offspring generation. These results support the hypothesis that the clustering characteristics of the MMS have familial components and point towards the influence of shared environment and genes in the aetiology of the multiple metabolic syndrome.

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