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ORIGINAL ARTICLE

Does the constellation of risk factors with and without abdominal adiposity associate with different cardiovascular mortality risk?

The DECODE Study Group

Aims: To evaluate whether the metabolic syndrome (MetS) defined by the International Diabetes Federation (IDF) criteria, which has abdominal adiposity as a mandatory element, predicts cardiovascular disease (CVD) mortality better than the cluster of other IDF-defined abnormalities not including abdominal adiposity.
Methods: Data from nine European population-based studies, including 7782 men and 7739 women (aged 30–89 years), with a median follow-up of 8.55 years, were jointly analyzed. Hazard ratios for CVD mortality were calculated with Cox regression models.
Results: In total, 41% of the men and 38% of the women had the IDF MetS. Individuals with the IDF MetS were by definition more obese and had a higher prevalence of diabetes than non-obese subjects with $\geqslant 2$ IDF abnormalities; whereas non-obese men with $\geqslant 3$ factors had more atherogenic lipid profiles. Multivariate adjusted hazard ratio for CVD death in men and women with the IDF MetS was 2.44 (1.69–2.98) and 2.32 (1.27–4.23); in non-obese men with 2 and $\geqslant 3$ factors the hazard ratio was 1.60 (1.12–2.30) and 2.44 (1.62–3.66), respectively, and in non-obese women with 2 factors the hazard ratio was 2.41 (1.09–5.33).
Conclusions: The cluster of the CVD risk factors predicted CVD mortality regardless of the presence or absence of the abdominal adiposity. Inclusion of abdominal adiposity as a prerequisite will miss those non-obese individuals who have increased CVD mortality.
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Keywords: metabolic syndrome; cardiovascular disease; mortality

Introduction

The International Diabetes Federation (IDF) proposed a new criteria for the metabolic syndrome (MetS) during the First International Congress on Prediabetes and Metabolic Syndrome on 14 April 2005.[1] These new IDF diagnostic criteria emphasized the importance of abdominal adiposity, as measured by waist circumference, considering it as a prerequisite for the definition; an ethnically specific waist cutoff value for abdominal adiposity and a low fasting plasma glucose cutoff value for impaired fasting glucose were recommended.

The IDF recommendation reflects the fact that obesity is the common component of the MetS and together with insulin resistance might be one of the underlying causes of the MetS.[1] It is, however, still unknown whether the cluster of cardiovascular disease (CVD) risk factors included in the definition of the MetS with abdominal adiposity has a different CVD mortality from that without obesity. This question was studied using the data from nine European Studies participating in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study.

Study populations and methods

The recruitment of the DECODE study has been described in detail previously.[2–8] Briefly, researchers who had performed European epidemiological studies on diabetes and abnormalities of glucose homeostasis, using a standard 2-h 75 g oral glucose tolerance test, were invited to participate. Individual data on fasting and 2-h glucose concentrations and a number of other variables were sent to the Diabetes and Genetic Epidemiology Unit of the National Public Health Institute in Helsinki, Finland, for the collaborative data analyses. All the studies involved in DECODE study were approved by the local ethical committee and informed consent was collected by the each centers. Agreement for the collaborating data analyses was collected from each center with the signature of the principal investigator.

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All the studies included in the current data analysis (Appendix 1 Table A1) are population-based. Except Uppsala study which only recruited men, all the studies comprised men and women. The CVD mortality was uniformly classified according to the International Classification of Disease 9 or 10. The glucose oxidase method for blood glucose and enzymatic method for lipid were applied in all study laboratories (Appendix 1 Table A1). Waist circumference was measured at the midway between the lower rib margin and iliac crest in all except the Cremona study, where it was measured at the level of umbilicus. Although the questionnaire to record the smoking status varied among centers, smoking status can be classified into non-smoker, current smoker or ex-smoker according to self-reported information.

Classification of subjects

Because the data on lipid-lowering medication was not available, a modified rather than the original IDF definition for the MetS was applied in the current study. Individuals were considered as having the IDF MetS if they had abdominal adiposity (waist girth $\geqslant$94 cm in men or $\geqslant$80 cm in women for Europid) plus any two of the following four abnormalities:

(1) Raised triglycerides: serum triglycerides $\geqslant$1.7 mM;
(2) reduced high-density lipoprotein cholesterol (HDL-c): HDL-c $<$1.03 mM in men and $<$1.29 mM in women;
(3) raised blood pressure: systolic blood pressure $\geqslant$130 mm Hg and/or diastolic blood pressure $\geqslant$85 mm Hg, or drug treatment of previously diagnosed hypertension and
(4) raised fasting plasma glucose: fasting plasma glucose $\geqslant$5.6 mM, or previously diagnosed type 2 diabetes.

Diabetes was defined as individuals with a prior history of diabetes or with fasting plasma glucose $\geqslant$7.0 mM and/or 2-h post-challenge glucose $\geqslant$11.1 mM.[9]

Statistical analysis

Because of the skewed distribution, plasma glucose, triglyceride and HDL-c were logarithmically transformed to get a near normal distribution and the geometric means were presented. The difference between groups was tested with analysis of variance and means were calculated with general linear model adjusting for age and study. The Cox proportional hazard model adjusted for age, study, serum cholesterol and smoking was performed to estimate hazard ratios for CVD death associated with the different clusters of metabolic abnormalities. All data analyses were performed with the SPSS for Windows 15.0 software package.

Results

A total of 15 521 subjects (7782 men and 7739 women) from nine studies participating in the DECODE study formed the present study population (Table 1). The mean age of study participants ranged from 47 to 71 years. The baseline examination was carried out around the beginning of 1990s, except for FINRISK 2002. The maximum length of follow-up ranged from 3.9 to 20.6 years. A total of 564 participants (436 men) died of CVD during the follow-up.

The IDF criteria defined 53.9% men and 62.9% women of the study population as having abdominal adiposity, and the prevalence of the IDF MetS was 41.2% in men and 37.9% in women (Table 2). In all, 20.3% men and 9.5% women had two or more abnormalities but without abdominal adiposity. Non-obese individuals with 3–4 (out of four) IDF MetS risk factors were rare.

Non-obese individuals with two IDF metabolic abnormalities had worse cardiovascular risk profiles than the non-obese subjects with one abnormality or less, but more favorable than those with the IDF MetS (Tables 2 and 3). Subjects with the IDF MetS were, by definition, more obese and also had higher blood pressure than the non-obese

Table 1 Demographic and follow-up information of the studies included

Studies	*No. of participants*	*Mean age (range), years*	*Sex (men), %*	*Baseline survey (year)*	*Response rate (%)*		*Follow-up (maximum), years*	*No. of CVD death (%)*	
					Baseline	*Follow-up*		*Men*	*Women*
Cremona, Italy	2042	59 (40–88)	44.0	1990–1991	58	100.0	6.9	30 (3.3)	24 (2.1)
MONICA, Finland, 1992	1855	54 (44–64)	45.3	1992	77	100.0	12.0	50 (5.9)	15 (1.5)
Hoorn, The Netherlands	2436	62 (49–77)	45.8	1989–1991	71	97.3	10.2	73 (6.5)	42 (3.2)
Newcastle, UK	749	55 (30–76)	51.1	1993–1994	96	100.0	10.6	25 (6.5)	8 (2.2)
MONICA, Poland	351	58 (44–73)	47.0	1992–1993	71	98.6	6.6	13 (7.9)	2 (1.1)
MONICA, Sweden, 1986	438	47 (30–64)	51.1	1986	82	100.0	20.6	25 (11.2)	8 (3.7)
MONICA, Sweden, 1992	697	47 (30–64)	47.5	1992	81	100.0	16.6	9 (2.7)	6 (1.6)
MONICA, Sweden, 1994	910	53 (30–74)	48.7	1994	77	100.0	12.6	19 (4.3)	11 (2.4)
Ely, UK	1026	54 (40–69)	41.4	1990–1992	74	99.2	15.7	21 (4.9)	6 (1.0)
Uppsala, Sweden	1161	71 (69–74)	100.0	1991–1995	65	100.0	12.4	142 (12.2)	—
FINRISK 2002, Finland	3856	58 (30–74)	46.6	2002	67	100.0	3.9	29 (1.6)	6 (0.3)
Total	15 521	58 (30–89)	41.4	—	—	—	20.6	436 (5.6)	128 (1.7)

Abbreviation: CVD, cardiovascular disease.

Table 2 Baseline characteristics of subjects with different clusters of metabolic abnormalities according to the IDF criteria

Metabolic abnormalities[a]	*Non-abdominal adiposity*			*Abdominal adiposity*	
	⩽1	*2*	*⩾3*	*⩽1*	*⩾2 (IDF MetS)*
Men					
No. (%) of subjects	1949 (25.0)	1082 (13.9)	495 (6.4)	1046 (13.4)	3210 (41.2)
Age (years)	56 (55.8–56.7)	58 (57.8–59.0)*†	58 (57.3–59.1)*†	59 (58.6–59.8)*	60 (59.7–60.4)*
Body mass index (kg m^{-2})	23.7 (23.6–23.8)	24.5 (24.3–24.6)*†	24.9 (24.7–25.2)*†	28.0 (27.8–28.2)*	29.4 (29.4–29.5)*
Waist (cm)	86 (85.5–86.1)	87 (87.1–87.9)*†	89 (88.3–89.5)*†	100 (99.9–100.7)*	104 (103.4–103.9)*
Systolic BP (mm Hg)	132 (130.8–132.4)	143 (141.5–143.7)*†	144 (142.1–145.4)*†	135 (134.1–136.3)*	147 (146.5–147.8)*
Diastolic BP (mm Hg)	78 (77.7–78.6)	83 (82.4–83.7)*†	84 (83.4–85.2)*†	82 (81.3–82.6)*	87 (86.8–87.6)*
Fasting glucose (mM)	5.21 (5.18–5.25)	5.75 (5.69–5.80)*†	6.08 (6.00–6.16)*	5.28 (5.24–5.33)	6.12 (6.08–6.15)*
2-h glucose (mM)	5.23 (5.15–5.32)	5.95 (5.82–6.08)*†	6.41 (6.21–6.62)*†	5.45 (5.33–5.57)*	6.85 (6.76–6.93)*
Cholesterol (mM)	5.73 (5.68–5.78)	5.88 (5.82–5.95)*†	6.16 (6.06–6.26)*†	5.80 (5.73–5.86)	6.01 (5.97–6.04)*
HDL-cholesterol (mM)	1.42 (1.40–1.43)	1.28 (1.27–1.30)*†	1.02 (1.00–1.05)*†	1.34 (1.32–1.36)*	1.11 (1.10–1.11)*
Triglyceride (mM)	1.00 (0.98–1.02)	1.30 (1.27–1.34)*†	2.19 (2.11–2.28)*†	1.13 (1.10–1.16)*	1.86 (1.83–1.89)*
Current smoker (%)	30.5 (28.5–32.6)	33.7 (30.9–36.6)†	34.3 (30.2–38.5)†	25.0 (22.3–27.6)*	26.6 (25.1–28.2)*
Women					
No. (%) of subjects	2140 (27.79)	565 (7.3)	167 (2.2)	1935 (25.0)	2932 (37.9)
Age (years)	52 (51.8–52.6)	57 (56.0–57.5)*†	60 (58.1–60.9)*	56 (56.0–56.8)*	60 (59.4–60.0)*
Body mass index (kg m^{-2})	22.9 (22.7–23.0)	23.5 (23.2–23.8)*†	23.5 (22.9–24.0)†	27.8 (27.7–28.0)*	30.0 (29.9–30.1)*
Waist (cm)	73 (72.8–73.5)	74 (73.2–74.5)†	75 (73.5–75.9)†	89 (88.3–89.0)*	94 (93.5–94.1)*
Systolic BP (mm Hg)	129 (128.3–130.0)	143 (141.1–144.2)*†	142 (138.9–144.7)*	134 (133.5–135.2)*	145 (144.7–146.1)*
Diastolic BP (mm Hg)	75 (74.4–75.4)	81 (80.5–82.3)*†	81 (79.1–82.4)*†	79 (78.5–79.5)*	84 (83.2–84.0)*
Fasting glucose (mM)	5.12 (5.08–5.15)	5.63 (5.57–5.70)*†	5.82 (5.70–5.95)*	5.13 (5.10–5.16)	5.91 (5.87–5.94)*
2-h glucose (mM)	5.32 (5.26–5.39)	6.02 (5.87–6.17)*†	6.51 (6.21–6.82)*	5.57 (5.49–5.64)*	6.84 (6.76–6.92)*
Cholesterol (mM)	5.90 (5.85–5.94)	6.02 (5.93–6.12)†	6.43 (6.26–6.62)*†	6.10 (6.05–6.15)*	6.19 (6.15–6.23)*
HDL-cholesterol (mM)	1.71 (1.69–1.73)	1.51 (1.49–1.54)*†	1.23 (1.19–1.27)*†	1.60 (1.58–1.61)*	1.29 (1.28–1.30)*
Triglyceride (mM)	0.93 (0.92–0.95)	1.15 (1.12–1.19)*†	1.81 (1.71–1.92)*†	1.06 (1.05–1.08)*	1.64 (1.62–1.66)*
Current smoker (%)	24.1 (22.3–25.9)	21.1 (17.7–24.4)	26.3 (19.7–33.0)	19.4 (17.6–21.1)*	20.1 (18.6–21.5)*

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome. Values are means (95% CI) adjusted for age and study except for noted. [a]Metabolic abnormalities defined by the IDF criteria, which include: (I) blood pressure ⩾130/85 mm Hg or treated hypertension; (II) triglyceride ⩾1.7 mM; (III) HDL-cholesterol <1.03 mM in men and <1.29 mM in women and (IV) fasting plasma glucose ⩾5.6 mM or previously diagnosed diabetes. $P<0.05$, *compared with non-obese subjects with ⩽1 abnormalities, †compared with subjects with the IDF MetS.

individuals with 3–4 abnormalities; but the lipid profiles were more atherogenic in the latter than in the former.

In non-obese men, the multivariate adjusted hazard ratio increased significantly with increasing number of factors clustered from 2 to 3–4 as compared with non-obese men with ⩽1 factor (reference group). This was also observed for non-obese women with two factors (Table 4). Compared with people with the IDF MetS, the hazard ratio was lower for non-obese men with two factors (0.45, 95% CI 0.34–0.59), but was not significantly different for non-obese men with 3–4 factors (1.09, 95% CI 0.77–1.54) and for non-obese women with two factors (1.04, 95% CI 0.58–1.92).

Discussion

Both the abdominal adiposity and IDF MetS were common in this study population, and the IDF MetS identified people with increased CVD mortality. Non-obese people with two or more IDF MetS factors were less prevalent, but they had higher CVD mortality compared with that in non-obese individuals with less IDF MetS

Table 3 Prevalence (%) of metabolic abnormalities in subjects with different clusters of abnormalities according to the IDF criteria

Metabolic abnormalities[a]	*Non-abdominal adiposity*			*Abdominal adiposity*	
	⩽1	*2*	*⩾3*	*1*	*⩾2 (IDF MetS)*
Men					
Raised blood pressure	47.1	83.3	89.7	56.9	93.2
Reduced HDL-c	4.3	21.1	61.6	4.1	38.8
Raised TG	4.5	28.3	87.1	5.4	58.1
Raised fasting plasma glucose	15.4	67.4	79.6	15.6	78.0
Women					
Raised blood pressure	37.9	87.3	93.4	54.6	90.9
Reduced HDL-c	7.0	28.8	68.9	7.9	52.1
Raised TG	2.2	18.9	74.9	3.2	50.4
Raised fasting plasma glucose	12.2	65.0	79.0	10.2	69.1

Abbreviations: HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; MetS, metabolic syndrome; TG, triglyceride. [a]Metabolic abnormalities defined by the IDF criteria, which include: (I) blood pressure ⩾130/85 mm Hg or treated hypertension; (II) triglyceride ⩾1.7 mM; (III) HDL-c <1.03 mM in men and <1.29 mM in women and (IV) fasting plasma glucose ⩾5.6 mM or previously diagnosed diabetes.

Table 4 Number of cardiovascular deaths, cumulative mortality and the hazard ratio in relation to different clusters of metabolic abnormalities according to the 2005 IDF definition of the MetS

Metabolic abnormalities[a]	*Non-abdominal adiposity*			*Abdominal adiposity*	
	⩽1	*2*	*⩾3*	*⩽1*	*⩾2 (IDF MetS)*
Men					
Number of death	62	57	38	56	223
Mortality (95% CI) per 1000 person years	3.3 (2.5–4.1)	6.0 (4.5–7.6)	8.6 (5.9–11.3)	5.9 (4.4–7.5)	8.6 (7.5–9.7)
Hazard ratio (95% CI)	1	1.60 (1.12–2.30)	2.44 (1.62–3.66)	1.45 (1.01–2.08)	2.24 (1.69–2.98)
Women					
Number of death	13	12	1	21	81
Mortality (95% CI) per 1000 person years	0.6 (0.3–0.9)	2.4 (1.0–3.7)	0.6 (−0.6 to 1.8)	1.3 (0.7–1.8)	3.4 (2.7–4.2)
Hazard ratio (95% CI)	1	2.41 (1.09–5.33)	NA	1.19 (0.59–2.40)	2.32 (1.27–4.23)

Abbreviations: HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; MetS, metabolic syndrome; NA, not available. Hazard ratio was estimated adjusting for age, study, total cholesterol and smoking. [a]Metabolic abnormalities defined by IDF criteria, which include: (I) blood pressure ⩾130/85 mm Hg or treated hypertension; (II) triglyceride ⩾1.7 mM; (III) HDL-c <1.03 mM in men and <1.29 mM in women and (IV) fasting plasma glucose ⩾5.6 mM, or previously diagnosed diabetes.

factors. The IDF definition of the MetS will miss these non-obese individuals and thus underestimate the CVD risk in the population.

The definition of the MetS aims at identifying high-risk individuals for CVD and type 2 diabetes.[1] However, evidence from studies that have assessed the association between the MetS and CVD risk is not consistent.[10] Some of them indicated that the MetS, defined with National Cholesterol Education Program (NCEP) or WHO criteria, is associated with significantly increased CVD risk, and might be a useful predictor for CVD events.[11–14] There are, however, also reports suggesting that the MetS did not convey a high CVD risk or had less power in predicting CVD events than the individual metabolic abnormality.[15–20] Our study revealed that the IDF criteria of the MetS predicted CVD mortality. By definition, subjects who did not have abdominal adiposity but had at least two other factors were not identified by the IDF criteria, while CVD mortality in such men was as high as in those with the IDF MetS even after adjusting age, smoking status and total serum cholesterol. In all, CVD deaths occurred in 22% men and 9% women in these non-obese individuals. The evidence from the present study suggests that the criteria without making a mandatory condition would be more inclusive of individuals with increased CVD mortality.

In this study population, non-obese men with two or more metabolic abnormalities had a higher prevalence of smoking than others. To check to what extent smoking has contributed to the increased CVD mortality in these men, stratified data analyses by smoking status were carried out. The hazard ratios for CVD mortality in non-obese men with two or more metabolic abnormalities as compared with non-obese men with zero or one abnormality were 1.83 (1.11–3.01) in smokers and 1.87 (1.09–3.23) in non-smokers. The corresponding figures in individuals with the IDF MetS were 2.21 (1.39–3.49) in smokers and 2.42 (1.52–3.84) in non-smokers, respectively. The results suggested that the increased CVD mortality could not be fully attributed to smoking status.

The merit of the collaborative data analysis is that the studies included in the current data analysis are all population-based and represent the general population of individual study location. The statistical power is higher than that of any single study alone, which can answer questions that may not be addressed in an individual study. The major problem of the collaborative data analysis is whether the data collected or the effect size is homogeneous since each study had been carried out individually using different protocols. We noticed, however, that laboratory analyses for glucose and lipids and the measurement of waist happened to be quite homogenous. And, the CVD mortality has been uniformly classified according to the International Classification of Disease. Moreover, a statistic measuring study-to-study variation showed that the effect size was not statistically different from zero ($P>0.10$).[21] In addition, adjustment for study was done in all the data analyses using pooled data.

In conclusion, the cluster of the CVD risk factors predicted CVD mortality regardless of whether the abdominal adiposity was present or not. Inclusion of abdominal adiposity as a prerequisite will miss many non-obese individuals who have increased CVD mortality.

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Conflict of interest
The authors state no conflict of interest.

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Appendix

Organization

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study was undertaken in 1997 upon the initiative of the European Diabetes Epidemiology Group.

Studies and investigators in this collaborative study were

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Table A1 Information on the blood sample, glucose and lipid assay, and waist measurement in individual studies involved in the current data analysis

Studies	*Blood sample for glucose*	*Glucose assay*	*Blood sample for lipid*	*Lipid assay*	*Waist measurement*
Cremona, Italy	Plasma	GOD-PAP glucose oxidase (Boehringer-Mannheim, Milan, Italy)	Plasma	Enzymatic techniques (Boehringer-Mannheim)	At the level of umbilicus
MONICA, Finland, 1992	Plasma	Glucose dehydrogenase	Serum	Liebermann–Burchard reaction and enzymatic techniques (Boehringer-Mannheim)	Midway between the lower rib margin and iliac crest
Hoorn, The Netherlands	Plasma	Glucose dehydrogenase (Merck, Darmstadt, Germany)	Serum	Enzymatic techniques (Boehringer-Mannheim)	Midway between the lower rib margin and iliac crest
Newcastle, UK	Plasma	Glucose oxidase (Hitachi 717 analyser)	Plasma	Enzymatic techniques. (Cobas Biocentrifugal analyser; Toch Products Ltd., UK)	Midway between the lower costal margin and the superior iliac crest
MONICA, Poland	Serum	Glucose oxidase (Express 550plus, CibaCorning)	Serum	Enzymatic techniques (Boehringer-Mannheim)	Midway between the lower rib margin and iliac crest
MONICA, Sweden, 1987, 1992, 1994	Plasma	Glucose oxidase (Beckman analyzer)	Serum	Enzymatic techniques (Boehringer-Mannheim)	Midway between the lower rib margin and iliac crest
Ely, UK	Plasma	Hexokinase assay	Plasma	Enzymatic techniques (RA 1000; Bayer Diagnostics, Basingstoke, Hants, UK)	Midway between the lower rib margin and iliac crest
Uppsala, Sweden	Plasma	Glucose dehydrogenase photospectrometric (Gluc-DH; Merck, Darmstadt, Germany)	Serum	Enzymatic techniques (Instrumentation Laboratories; Lexington; USA) HDL particles were separated by precipitation with magnesium chloride/phosphotungstate	Midway between the lowest rib and the iliac crest
FINRISK 2002, Finland	Plasma	Hexokinase assay (Thermo Electron Oy)	Serum	Enzymatic techniques (CHOD/PAP), Optima, Thermo Electron Oy	Midway between the lower rib margin and iliac crest