

Metabolically Healthy Obesity is Associated with Incident Chronic Kidney Disease in the General Population

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Introduction

Obesity and metabolic abnormalities have become a growing concern in the general population. Recent studies have suggested that obese individuals without metabolic abnormalities exhibit a low cardiovascular risk similarly to non-obese healthy individuals. However, it is unknown on the relationship between such different phenotypes and the development of chronic kidney disease (CKD).

Methods

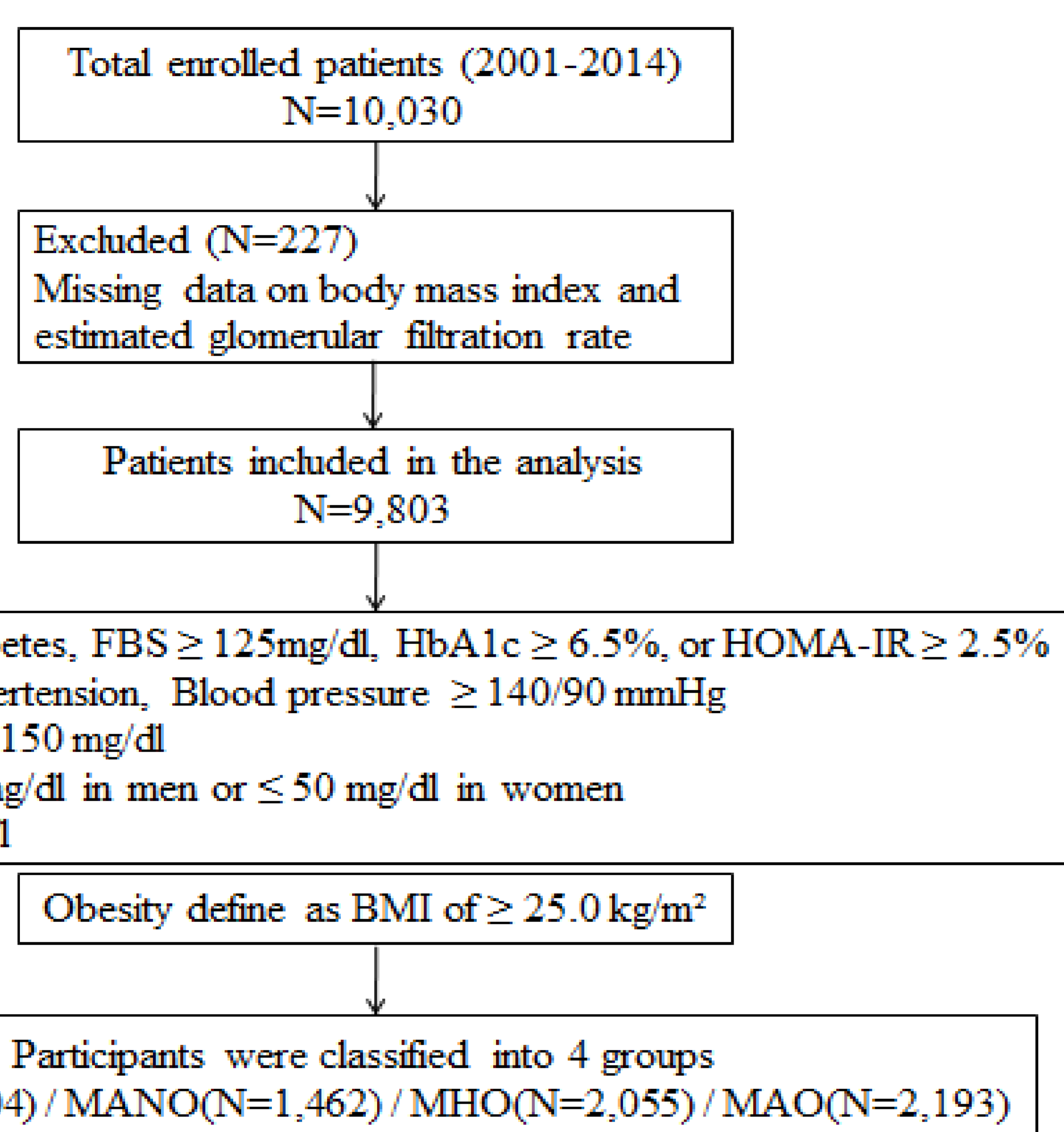


Figure 1. A flow diagram of study subjects

We used five clinical categories to define metabolic status; 1) HbA1c \geq 6.5%, history of diabetes, fasting blood glucose \geq 125mg/dL or homeostatic model assessment-insulin resistance \geq 2.5%, 2) triglyceride \geq 150 mg/dL, 3) high-density lipoprotein cholesterol \leq 40 mg/dL in men or \leq 50 mg/dL in women, 4) high-sensitivity C-reactive protein \geq 1 mg/L, or 5) history of hypertension, systolic or diastolic blood pressure \geq 140/90 mmHg. Participants who met \geq 3 categories were considered metabolically unhealthy. Obesity was defined as a body mass index of \geq 25.0 kg/m². Based on the criteria of metabolic abnormality and obesity, participants were classified into 4 groups. The study endpoint was an onset of incident CKD, which was defined as an eGFR of \leq 60 ml/min per 1.73m² for at least \geq 2 measurements during follow-up period.

Results

Table 1. Characteristics of study participants at baseline

Characteristic [⊖]	Overall [⊖]	Non-obese [⊖]		Obese [⊖]		P-value [⊖]
		MHNO ^a	MANO ^b	MHO ^c	MAO ^d	
Participants, n (%) [⊖]	9,803 [⊖]	4,094 (41.8) [⊖]	1,461(14.9) [⊖]	2,055 (21.0) [⊖]	2,193(22.4) [⊖]	- [⊖]
Age (year) [⊖]	52.0 \pm 8.8 [⊖]	51.0 \pm 8.8 [⊖]	55.4 \pm 9.0 [⊖]	50.2 \pm 8.0 [⊖]	53.5 \pm 8.5 [⊖]	<0.001 [⊖]
Men, n (%) [⊖]	4,666 (47.6) [⊖]	2,080 (50.8) [⊖]	727 (49.8) [⊖]	934 (45.5) [⊖]	925 (42.2) [⊖]	<0.001 [⊖]
Smoking, n (%) [⊖]	4,010 (40.9) [⊖]	1,774 (43.3) [⊖]	662 (45.3) [⊖]	760 (37.0) [⊖]	814 (37.1) [⊖]	<0.001 [⊖]
Body mass index (kg/m ²) [⊖]	24.5 \pm 3.1 [⊖]	22.2 \pm 1.8 [⊖]	22.8 \pm 1.6 [⊖]	27.0 \pm 1.8 [⊖]	27.7 \pm 2.2 [⊖]	<0.001 [⊖]
Hypertension, n (%) [⊖]	1,446 (14.8) [⊖]	187 (4.6) [⊖]	348 (23.8) [⊖]	154 (7.5) [⊖]	757 (34.5) [⊖]	<0.001 [⊖]
Diabetes, n (%) [⊖]	646 (6.6) [⊖]	83 (2.0) [⊖]	235 (16.1) [⊖]	46 (2.2) [⊖]	282 (12.9) [⊖]	<0.001 [⊖]
Cerebrovascular accident, n (%) [⊖]	105 (1.1) [⊖]	36 (0.9) [⊖]	21 (1.4) [⊖]	14 (0.7) [⊖]	34 (1.6) [⊖]	0.012 [⊖]
Congestive heart failure, n (%) [⊖]	21 (0.2) [⊖]	9 (0.2) [⊖]	1 (0.1) [⊖]	3 (0.1) [⊖]	9 (0.4) [⊖]	0.057 [⊖]
Coronary artery disease, n (%) [⊖]	71 (0.7) [⊖]	24 (0.6) [⊖]	5 (0.1) [⊖]	18 (0.9) [⊖]	24 (1.1) [⊖]	0.031 [⊖]

SBP [⊖] (mmHg) [⊖]	121.4 \pm 18.4 [⊖]	115.0 \pm 16.0 [⊖]	129.3 \pm 19.3 [⊖]	117.5 \pm 14.9 [⊖]	131.7 \pm 18.5 [⊖]	<0.001 [⊖]
DBP [⊖] (mmHg) [⊖]	80.2 \pm 11.4 [⊖]	76.2 \pm 10.2 [⊖]	84.0 \pm 11.4 [⊖]	78.7 \pm 10.0 [⊖]	86.6 \pm 11.1 [⊖]	<0.001 [⊖]
MAP [⊖] (mmHg) [⊖]	107.7 \pm 15.5 [⊖]	102.1 \pm 13.5 [⊖]	114.2 \pm 15.9 [⊖]	104.6 \pm 12.7 [⊖]	116.6 \pm 15.3 [⊖]	<0.001 [⊖]
Hemoglobin (g/dl) [⊖]	13.5 \pm 1.5 [⊖]	13.3 \pm 1.5 [⊖]	13.7 \pm 1.5 [⊖]	13.6 \pm 1.6 [⊖]	13.7 \pm 1.5 [⊖]	<0.001 [⊖]
Blood urea nitrogen (mg/dl) [⊖]	14.2 \pm 3.5 [⊖]	14.1 \pm 3.6 [⊖]	14.1 \pm 3.5 [⊖]	14.4 \pm 3.5 [⊖]	14.3 \pm 3.5 [⊖]	0.003 [⊖]
Creatinine (mg/dL) [⊖]	0.8 \pm 0.1 [⊖]	0.8 \pm 0.1 [⊖]	0.8 \pm 0.1 [⊖]	0.8 \pm 0.1 [⊖]	0.8 \pm 0.1 [⊖]	<0.001 [⊖]
eGFR (ml/min per 1.73 m ²) [⊖]	92.8 \pm 13.1 [⊖]	94.4 \pm 12.9 [⊖]	91.4 \pm 12.4 [⊖]	92.5 \pm 13.6 [⊖]	91.0 \pm 12.8 [⊖]	<0.001 [⊖]
Fasting Blood Glucose (mg/dl) [⊖]	87.1 \pm 21.2 [⊖]	82.7 \pm 12.4 [⊖]	93.3 \pm 33.7 [⊖]	84.5 \pm 12.8 [⊖]	94.4 \pm 27.0 [⊖]	<0.001 [⊖]
Total cholesterol (mg/dl) [⊖]	190.8 \pm 35.5 [⊖]	182.6 \pm 33.3 [⊖]	195.4 \pm 37.4 [⊖]	190.8 \pm 34.0 [⊖]	202.7 \pm 35.7 [⊖]	<0.001 [⊖]
Triglyceride (mg/dl) [⊖]	161.9 \pm 105.0 [⊖]	122.5 \pm 66.5 [⊖]	209.5 \pm 121.7 [⊖]	144.7 \pm 83.1 [⊖]	219.9 \pm 128.8 [⊖]	<0.001 [⊖]
HDL-C (mg/dl) [⊖]	44.6 \pm 10.0 [⊖]	47.5 \pm 10.4 [⊖]	43.2 \pm 9.9 [⊖]	43.9 \pm 9.2 [⊖]	40.9 \pm 8.4 [⊖]	<0.001 [⊖]
Albumin (g/dl) [⊖]	4.2 \pm 0.3 [⊖]	4.2 \pm 0.3 [⊖]	4.2 \pm 0.3 [⊖]	4.2 \pm 0.3 [⊖]	4.2 \pm 0.3 [⊖]	0.293 [⊖]
Calcium (mg/dl) [⊖]	9.6 \pm 0.4 [⊖]	9.5 \pm 0.4 [⊖]	9.6 \pm 0.4 [⊖]	9.5 \pm 0.4 [⊖]	9.6 \pm 0.4 [⊖]	<0.001 [⊖]
Sodium (mmol/l) [⊖]	142.5 \pm 2.1 [⊖]	142.4 \pm 2.1 [⊖]	142.5 \pm 2.3 [⊖]	142.5 \pm 2.1 [⊖]	142.6 \pm 2.1 [⊖]	0.054 [⊖]
Potassium (mmol/l) [⊖]	4.4 \pm 0.4 [⊖]	4.4 \pm 0.3 [⊖]	4.5 \pm 0.4 [⊖]	4.4 \pm 0.4 [⊖]	4.4 \pm 0.4 [⊖]	<0.001 [⊖]
Chloride (mmol/l) [⊖]	102.9 \pm 2.3 [⊖]	103.1 \pm 2.3 [⊖]	102.5 \pm 2.5 [⊖]	103.2 \pm 2.2 [⊖]	102.7 \pm 2.4 [⊖]	<0.001 [⊖]
HbA1c (%) [⊖]	5.7 \pm 0.9 [⊖]	5.5 \pm 0.5 [⊖]	6.1 \pm 1.3 [⊖]	5.6 \pm 0.5 [⊖]	6.1 \pm 1.1 [⊖]	<0.001 [⊖]
HOMA-IR [⊖]	1.6 \pm 1.2 [⊖]	1.3 \pm 0.8 [⊖]	1.7 \pm 1.94 [⊖]	1.5 \pm 0.9 [⊖]	2.1 \pm 1.5 [⊖]	<0.001 [⊖]
hs-CRP (mg/l) [⊖]	1.4 [0.7-2.5] [⊖]	1.0 [0.4-1.9] [⊖]	1.8 [1.3-2.9] [⊖]	1.1 [0.5-2.2] [⊖]	2.1 [1.4-3.4] [⊖]	<0.001 [⊖]

Smoking was defined as never and current or former smokers. Abbreviations: HOMA-IR^{*}, homeostatic model assessment-insulin resistance; MHNO^a, metabolically healthy non-obese; MANO^b, metabolically abnormal non-obese; MHO^c, metabolically healthy obese; MAO^d, metabolically abnormal obese; SBP[⊖]: systolic blood pressure, DBP[⊖]: diastolic blood pressure, MAP[⊖]: mean arterial pressure. [⊖]

Table 2. Hazard ratios for renal outcome according to metabolic phenotypes

	MHNO ^a	MANO ^b	MHO ^c	MAO ^d
Incidence of outcome (n/n) [⊖]	220/4,094 [⊖]	192/1,461 [⊖]	151/2,055 [⊖]	279/2,193 [⊖]
Model 1 [⊖]	1.000 [⊖] (Reference) [⊖]	2.744 [⊖] (2.261 to 3.331) [⊖]	1.350 [⊖] (1.097 to 1.661) [⊖]	2.518 [⊖] (2.110 to 3.005) [⊖]
P-value	- [⊖]	<0.001 [⊖]	0.005 [⊖]	<0.001 [⊖]
Model 2 [⊖]	1.000 [⊖] (Reference) [⊖]	1.511 [⊖] (1.227 to 1.861) [⊖]	1.294 [⊖] (1.047 to 1.600) [⊖]	1.511 [⊖] (1.299 to 1.858) [⊖]
P-value	- [⊖]	<0.001 [⊖]	0.015 [⊖]	<0.001 [⊖]

Model 1[⊖]: a crude analysis without adjustment. [⊖]

Model 2[⊖]: a full adjusted model including gender, sex, history of hypertension, diabetes, smoking status (never and current or former), mean arterial pressure, hemoglobin, albumin, eGFR, HDL-C, hs-CRP, HOMA-IR, and proteinuria [⊖]

Abbreviations: MHNO^a, metabolically healthy non-obese; MANO^b, metabolically abnormal non-obese; MHO^c, metabolically healthy obese; MAO^d, metabolically abnormal obese. [⊖]

The mean age was 52.0 years and 4,666 (47.6 %) were males. During a mean follow-up duration of 8.36 years, primary endpoint occurred in 843 (8.5%) participants; 279 (12.7%), 192 (13.1%), 151 (7.3%), and 220 (5.3%) in MAO, MANO, MHO, and MHNO groups, respectively (P < 0.001). In a multivariable Cox regression after adjustment of confounding factors, MAO [hazard ratio (HR), 1.511; 95% confidence interval (CI), 1.22-1.85; P<0.001] and MANO (HR, 1.511; 95% CI, 1.22-1.86; P<0.001) phenotypes were associated with increased risks of incident CKD as compared to MHNO phenotype. In addition, MHO group had a higher risk of CKD development (HR, 1.294; 95% CI, 1.04-1.60; P=0.017) than MHNO group, but comparable risk to MAO and MANO groups.

Conclusion

This study showed that metabolically abnormal phenotypes irrespective of obesity portend a worse prognosis for newly developed CKD. In addition, MHO phenotype is also associated with incident CKD, raising a concern against previous notion that MHO is 'healthy' in the general population.