

# Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness

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## ABSTRACT

Metabolic syndrome is defined as a cluster of glucose intolerance, hypertension, dyslipidemia and central obesity with insulin resistance as the source of pathogenesis. Although several different combinations of criteria have been used to define metabolic syndrome, a recently published consensus recommends the use of ethnic-specific criteria, including waist circumference as an indicator of central obesity, triglyceride and high-density lipoprotein (HDL) cholesterol as indicators of dyslipidemia, and blood pressure greater than 130/85 mmHg. The definition of dysglycemia, and whether central obesity and insulin resistance are essential components remain controversial. Regardless of the definition, the prevalence of metabolic syndrome is increasing in Western and Asian countries, particularly in developing areas undergoing rapid socioenvironmental changes. Numerous clinical trials have shown that metabolic syndrome is an important risk factor for cardiovascular disease (CVD), type 2 diabetes mellitus and all-cause mortality. Therefore, metabolic syndrome might be useful as a practical tool to predict these two major metabolic disorders. Comprehensive management of risk factors is very important to the improvement of personal and public health. However, recent studies have focused on the role metabolic syndrome plays as a risk factor for CVD; its importance in the prediction of incident diabetes is frequently overlooked. In the present review, we summarize the known evidence supporting metabolic syndrome as a predictor for type 2 diabetes mellitus and CVD. Additionally, we suggest how metabolic syndrome might be useful in clinical practice, especially for the prediction of diabetes. (*J Diabetes Invest*, doi: 10.1111/jdi.12075, 2013)

**KEY WORDS:** Metabolic syndrome, Risk factor, Type 2 diabetes mellitus

## INTRODUCTION

The clustering of glucose intolerance, hypertension, dyslipidemia and obesity, particularly central obesity, has been termed metabolic syndrome<sup>1–3</sup>. Ever since metabolic syndrome was described by Reaven<sup>4</sup> in 1988, various definitions have been published and revised, and numerous studies have explored its pathophysiology. When the concept of metabolic syndrome was first proposed, the primary pathological process was believed to be insulin resistance or hyperinsulinemia<sup>5–8</sup>. In addition, many etiological factors have been linked to the development and progression of metabolic syndrome, including an altered inflammatory state<sup>9,10</sup>, visceral adipose tissue abnormalities<sup>11</sup>, and the activation of the sympathetic nervous system<sup>12</sup>.

Although metabolic syndrome contains several unresolved matters, including ambiguous criteria, the inclusion of diabetes, a unifying mechanism and its role as a 'syndrome'<sup>13</sup>, its worldwide

prevalence has increased rapidly into one of the biggest health problems. Metabolic syndrome is known to increase cardiovascular morbidity and mortality, type 2 diabetes, and all-cause mortality<sup>14</sup>. The desired clinical response to metabolic syndrome is improved individual and national public health, and a mitigation of negative outcomes through comprehensive management.

Most studies agree that cardiovascular disease (CVD) is the major outcome of metabolic syndrome<sup>15–17</sup>. However, whether type 2 diabetes mellitus is also a major outcome of metabolic syndrome or one of its components is a topic of debate. Many reports have confirmed a strong relationship between metabolic syndrome and incident diabetes.

The present review describes various definitions and changes in the prevalence of the metabolic syndrome, and the significance of metabolic syndrome as a risk factor of type 2 diabetes mellitus and CVD. Finally, we propose the clinical usefulness inherent to metabolic syndrome, especially as a predictor of incident diabetes.

## VARIOUS DEFINITIONS OF THE METABOLIC SYNDROME

Although most medical communities agree that obesity, hypertension, dyslipidemia and abnormal glucose tolerance should be

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factored into the diagnosis, no standard criteria have been set for metabolic syndrome. Several clinical definitions have been proposed and used in clinical practice (Table 1).

The first formalized definition of metabolic syndrome was introduced in 1998 by a group who was consulted by the World Health Organization (WHO) for a definition of diabetes<sup>1</sup>. The diagnostic criteria included markers of abnormal glucose metabolism or insulin resistance, plus at least two out of four risk factors, which included obesity, hypertension, elevated triglycerides and/or reduced high-density lipoprotein (HDL) cholesterol, and microalbuminuria. Insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) or the euglycemic hyperinsulinemic clamp technique, is a key factor of the WHO diagnostic criteria that does not exclude type 2 diabetes mellitus. The diagnostic criteria posed by the European Group for the Study of Insulin Resistance (EGIR) in 1999<sup>2</sup> and by American Association of Clinical Endocrinologists (AACE) in 2003<sup>18</sup> also emphasized the presence of insulin resistance. In the three aforementioned definitions listed, both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were noted as markers of abnormal glucose metabolism. However, in contrast to the WHO definition, patients with type 2 diabetes were not included in the EGIR and AACE criteria.

The most commonly used criteria emerged from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) in 2001<sup>3</sup>. The presence of three of the five risk factors warrants a metabolic syndrome diagnosis. Under the direction of the American Diabetes Association (ADA), the definition of dysglycemic factor was changed from a fasting plasma glucose (FPG) higher than 110 mg/dL in 2001 to a FPG higher than 100 mg/dL in 2006<sup>19</sup>. The International Diabetes Federation (IDF), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) define metabolic syndrome as central obesity based on waist circumference plus two or more additional metabolic risk factors<sup>20,21</sup>. Central obesity criteria were revised in 2005 and 2009; they applied different classification criteria based on ethnicity and risk factor status of CVD. Type 2 diabetes is included; however, the IGT criteria are not in NCEP or IDF. These approaches possess the strength of simplicity and the practicality of their components. In contrast, these approaches are limited, because they underestimate the prevalence of IGT and insulin resistance<sup>14</sup>.

### PREVALENCE OF METABOLIC SYNDROME

The worldwide prevalence of metabolic syndrome is increasing. In the USA, age-adjusted prevalence increased from 29.2% in the National Health and Nutrition Examination Survey (NHANES) III to 34.2% in NHANES 1999–2006<sup>22</sup>. Prevalence is significantly higher in women, especially younger women aged 20–39 years. This increasing trend has been observed in Asian countries as well. Age-adjusted prevalence in the South Korea NHANES (KNHANES) 1998 was 24.9%, and increased

to 31.3% in the KNHANES 2007 with the application of revised NCEP criteria<sup>23</sup>. Distinct and rapid increases in prevalence occur in women aged at least 50 years, after menopause, whereas metabolic syndrome in men aged at least 60 years decreases gradually; and the prevalence in adolescents increased from 6.8% in KNHANES 1998 to 9.2% in KNHANES 2001<sup>24</sup>, to 13.0% in KNHANES 2005<sup>25</sup>. In China, the prevalence of metabolic syndrome increased persistently as well<sup>26</sup>.

Variance in the prevalence is a result of the use of differing criteria and inclusion of different ethnicities. In a meta-analysis in 2007, Nestel *et al.*<sup>27</sup> reported prevalence ranges of 10–30% in several Asian countries, including South Korea, China, Singapore, Taiwan, Hong Kong and the Philippines. For Japan, the diagnostic criteria for central obesity differ from other Asian countries, with waist circumference measurements of more than 85 cm for males and 90 cm for females. Based on this definition, prevalence was 22.8% for men and 8.7% for women in the Japanese National Health and Nutrition Survey (NHNS) 2003<sup>28</sup>. However, when other criteria were applied (waist circumference  $\geq 85$  cm for males and  $\geq 80$  cm for females), the prevalence in females was increased from 8.7 to 19.2%. The prevalence of metabolic syndrome was 22.0% based on IDF, 16.9% based on NCEP and 23.3% based on modified NCEP criteria from the Nantong Metabolic Syndrome Study (NMSS) that was carried out in China in 2007–2008<sup>26</sup>.

### METABOLIC SYNDROME AS A PREDICTOR OF CVD

Numerous studies have confirmed the prognostic significance of metabolic syndrome on cardiovascular outcomes, including some negative results (Table 2).

The results of the Botnia study on 4,483 middle-aged participants in Finland and Sweden showed a marked increase in cardiovascular mortality in participants with metabolic syndrome during a 6.9-year follow-up period (12.0 vs 2.2%,  $P < 0.001$ )<sup>15</sup>. In the Kuopio Ischemic Heart Disease Risk Factor Study, metabolic syndrome was associated with a 2.5 to 2.8-fold greater risk of death from any cardiovascular cause<sup>29</sup>. However, the relative risks (RR) and statistical significance varied with differing definitions of metabolic syndrome. The RR associated with WHO definitions was significant in all adjustment models; however, when the NCEP criteria (waist circumference over 94 cm) were used, no statistical significance was found in the association between RR and CVD mortality after adjustment for conventional risk factors, such as age, examination year, low-density lipoprotein (LDL) cholesterol, smoking status and family history of coronary heart disease. A meta-analysis on the 87 studies that used NCEP or revised NCEP definitions confirmed that metabolic syndrome is associated with a twofold increase in cardiovascular outcomes<sup>17</sup>. The RR was 2.35 (95% confidence interval [CI] 2.02–2.73) for all CVD, 2.40 (95% CI 1.87–3.08) for CVD mortality, 1.99 (95% CI 1.61–2.46) for myocardial infarction and 2.27 (95% CI 1.80–2.85) for stroke. A few studies on Asian populations produced similar results<sup>30,31</sup>. The Hisayama Study, 14-year prospective study that

**Table 1** | Various definitions of metabolic syndrome

	WHO (1998) <sup>1</sup>	EGR (1999) <sup>2</sup>	NCEP-ATP III (2001) <sup>3</sup>	AACE (2003) <sup>18</sup>	IDF (2005) <sup>20</sup>	IDF (2009) <sup>21</sup>
<b>Definition</b>	Type 2 diabetes, IFG, IGT or insulin resistance plus at least two of the criteria below	Fasting hyperinsulinemia (highest 25%), plus at least two criteria below	At least three criteria below	Specific clinical factors* plus at least two criteria below	Central obesity plus at least two criteria below	At least three criteria below
<b>Glucose</b>	IFG, IGT, type 2 diabetes	FPG $\geq 6.1$ mmol/L (excludes diabetes)	FPG $\geq 110$ mg/dL (includes diabetes; FPG $\geq 100$ mg/dL, modified in 2006)	IFG (FPG 110–125 mg/dL) or IGT (excludes diabetes)	FPG $\geq 100$ mg/dL (includes diabetes)	FPG $\geq 100$ mg/dL (includes diabetes)
<b>Abdominal obesity</b>	WHR $>0.9$ in men and $>0.85$ in women or BMI $>30$ kg/m <sup>2</sup>	WC $\geq 94$ cm in men and $\geq 80$ cm in women	WC $>102$ cm in men and $>88$ cm in women	BMI $\geq 25$ kg/m <sup>2</sup>	Ethnic-specific definition <sup>†</sup>	Population- and country-specific definition <sup>†</sup>
<b>BP</b>	BP $\geq 140/90$ mmHg	BP $\geq 140/90$ mmHg or treated for hypertension	BP $\geq 130/85$ mmHg or treated for hypertension	BP $\geq 130/85$ mmHg	BP $\geq 130/85$ mmHg or treated for hypertension	BP $\geq 130/85$ mmHg or treated for hypertension
<b>TG</b>	TG $\geq 150$ mg/dL and/or HDL-C $<35$ mg/dL in men	TG $\geq 150$ mg/dL or $<39$ mg/dL or treated for dyslipidemia	TG $\geq 150$ mg/dL or treated for dyslipidemia	TG $>150$ mg/dL	TG $\geq 150$ mg/dL or treated for dyslipidemia	TG $\geq 150$ mg/dL or treated for dyslipidemia
<b>HDL-C</b>	And HDL-C $<39$ mg/dL in women	HDL-C $<40$ mg/dL in men or HDL-C $<50$ mg/dL in women or treated for dyslipidemia	HDL-C $<40$ mg/dL in men or HDL-C $<50$ mg/dL in women or treated for dyslipidemia	HDL-C $<40$ mg/dL in men or HDL-C $<50$ mg/dL in women	HDL-C $<40$ mg/dL in men or HDL-C $<50$ mg/dL in women or treated for dyslipidemia	HDL-C $<40$ mg/dL in men or HDL-C $<50$ mg/dL in women or treated for dyslipidemia
<b>Other</b>		Microalbuminuria (UAER $>20$ $\mu$ g/min)				

AAACE, American Association of Clinical Endocrinologists; BMI, body mass index; BP, blood pressure; EGR, European Group for the Study of Insulin Resistance; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; TG, triglyceride; UAER, urinary albumin excretion rate; WHO, World Health Organization; WHR, waist-to-hip ratio. \*Diagnosis of cardiovascular diseases (CVD), hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease, or acanthosis nigricans; family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-Caucasian ethnicity; sedentary lifestyle; waist circumference (WC)  $>40$  inches in men and WC  $>35$  inches in women; age  $>40$  years. <sup>†</sup>Europe,  $\geq 94$  cm in men and  $\geq 80$  cm in women; South Asian and Chinese,  $\geq 90$  cm in men and  $\geq 80$  cm in women; Japanese,  $\geq 85$  cm in men and  $\geq 90$  cm in women; South and Central America, South Asian recommendations until more specific data become available; Sub-Saharan Africa, Eastern Mediterranean and Middle East populations, European data until more specific data becomes available. <sup>‡</sup>WC thresholds are recommended based on organization and risk of metabolic complications.

**Table 2** | Metabolic syndrome and relative risk of cardiovascular disease

References	Year	Definition	Population	n	F/U (years)	Adjusted RR (95% CI)
Wilson <i>et al.</i> <sup>62</sup>	1999	≥3 of the 6 metabolically linked risk factors	Framingham Offspring Study (USA population; age 18–74 years)	2,406 men and 2,569 women	16.0	2.39 (1.56–3.36) in men 5.90 (2.54–13.73) in women
Isomaa <i>et al.</i> <sup>15</sup>	2001	WHO	Botnia Study in Finland and Sweden, including diabetes (age 35–70 years)	3,928	6.9	2.96 (2.36–3.72)
Lakka <i>et al.</i> <sup>29</sup>	2002	WHO NCEP	Kuopio Ischemic Heart Disease Risk Factor Study (Finnish men without diabetes; age 42–60 years)	1,209	11.4	2.83 (1.43–5.59) 2.27 (0.96–5.36)
Resnick <i>et al.</i> <sup>63</sup>	2003	NCEP	Strong Heart Study (non-diabetic American Indians)	2,283	7.6	1.11 (0.79–1.56)
Malik <i>et al.</i> <sup>64</sup>	2004	Modified NCEP	United States population in NHANES II (age 30–75 years)	6,255	13.3	2.02 (1.42–2.89)
Hu <i>et al.</i> <sup>65</sup>	2004	Modified WHO	DECODE study (participants of 11 prospective European cohort studies without diabetes; age 30–89 years)	6,156 men and 5,356 women	8.8	2.26 (1.61–3.17) in men 2.78 (1.57–4.94) in women
Wilson <i>et al.</i> <sup>33</sup>	2005	NCEP	Framingham Offspring Study (Fourth examination of the cohort excluding diabetes; age 22–81 years)	3,323	8.0	2.88 (1.99–4.16)
Takeuchi <i>et al.</i> <sup>66</sup>	2005	Modified NCEP	Tanno and Sobetsu Study (middle-aged Japanese men excluding diabetes)	808	6.0	2.23 (1.14–4.34)
Andreadis <i>et al.</i> <sup>67</sup>	2007	NCEP	Mediterranean hypertensive population including diabetes	1,007	2.1	2.26 (1.27–4.02)
Meig <i>et al.</i> <sup>46</sup>	2007	EGIR NCEP IDF	Framingham Offspring Study (Fifth examination cohort participants)	2,803	11.6	2.0 (1.6–2.7) 1.3 (0.9–1.9) no IR group 2.3 (1.7–3.1) IR group 1.6 (1.1–2.2) no IR group 2.2 (1.6–3.0) IR group
Song <i>et al.</i> <sup>68</sup>	2007	Modified NCEP	Women's Health Study (female adults, age ≥45 years)	25,626	10.0	2.40 (1.71–3.37) in BMI <25 3.01 (2.30–3.94) in BMI 25–29.9 2.89 (2.19–3.80) in BMI ≥30 1.61 (1.12–2.33)
Ingeisson <i>et al.</i> <sup>69</sup>	2007	NCEP	Framingham Offspring Study (Sixth examination cohort participants)	1,945	7.2	1.86 (1.32–2.62) in men 1.70 (1.22–2.36) in women
Ninomiya <i>et al.</i> <sup>30</sup>	2007	NCEP	Hisayama Study (Japanese including diabetes; age ≥40 years)	2,452	14.0	1.75 (1.27–2.41) in men 1.90 (1.31–2.77) in women 2.92 (1.54–5.55) in men under 60 years
Kokubo <i>et al.</i> <sup>70</sup>	2008	Modified NCEP Japanese	Urban Japanese (age 30–79 years)	5,332	11.5	1.98 (1.3–3.03) in men 4.14 (1.78–9.14) in women 1.63 (1.11–2.37) in BMI <25 1.74 (1.32–2.30) in BMI 25–29.9 2.55 (1.82–3.58) in BMI ≥ 30
Hwang <i>et al.</i> <sup>31</sup>	2009	Modified NCEP	Korean (age 20–78 years)	2,435	8.7	1.63 (1.11–2.37) in BMI <25 1.74 (1.32–2.30) in BMI 25–29.9 2.55 (1.82–3.58) in BMI ≥ 30
Arnlov <i>et al.</i> <sup>71</sup>	2010	Modified NCEP	Uppsala Longitudinal Study of adult men (ULSAM) without diabetes (age 50 years)	1,758	30.0	1.63 (1.11–2.37) in BMI <25 1.74 (1.32–2.30) in BMI 25–29.9 2.55 (1.82–3.58) in BMI ≥ 30

CI, confidence interval; BMI, body mass index; EGIR, European Group for the Study of Insulin Resistance; F/U, follow-up period; IDF, International Diabetes Federation; IR, insulin resistance; NCEP, National Cholesterol Education Program; NHANES, National Health and Nutrition Examination Survey; RR, relative risks; WHO, World Health Organization.

included 2,452 middle-aged Japanese individuals, confirmed that the hazard ratio (HR) of CVD events was 1.86 (95% CI 1.32–2.62) in men with metabolic syndrome and 1.70 (95% CI 1.22–2.36) in women, after multivariable adjustment<sup>30</sup>.

CVD predictability tended to vary by sex and numbers of components<sup>31–33</sup>. Wilson *et al.*<sup>32</sup> determined that the RR of coronary heart diseases was significantly higher in women than in men, although they did share the same number of metabolic risk factors. In that study, the presence of three or more metabolic risk factors increased the risk for coronary heart diseases (CHD) 2.5-fold in men and approximately sixfold in women during the 16-year follow-up period of middle-aged adults. In the presence of two risk factors, the RR was approximately 2.0 in men and 3.0 in women. A study of 2,435 Korean participants (age range 20–78 years) showed that the odds ratios (OR) for CVD were higher in women (OR 4.04; 95% CI 1.78–9.14) than in men (OR 1.98; 95% CI 1.30–3.03)<sup>31</sup>. In the Beaver Dam Study, the incidence of CVD was 2.5% in a group to have 0 components of the metabolic syndrome by WHO definition and 14.9% in four more risk factors<sup>16</sup>. The OR was 1.95 (95% CI 0.91–4.16) in the group with one risk factor, 2.05 (95% CI 0.96–4.40) in the group with two risk factors, 2.70 (95% CI 1.22–5.98) in the group with three risk factors and 5.86 (95% CI 2.51–13.66) in the group with four or more risk factors. In the Framingham Heart Study Offspring Study, the age-adjusted RR for CVD gradually increased as the number of risk factors increased in both men and women<sup>33</sup>. In men, the RR was 1.48 (95% CI 0.69–3.16) for one or two components and 3.99 (95% CI 1.89–8.41) for three or more components. In women, the RR was 3.39 (95% CI 1.31–8.81) for one or two components and 5.95 (95% CI 2.20–16.11) for three or more components.

## METABOLIC SYNDROME AS A PREDICTOR OF TYPE 2 DIABETES

Many large-scale clinical trials and meta-analyses reported that the presence of metabolic syndrome, regardless of definition, was highly predictive of new-onset type 2 diabetes in many different populations (Table 3). Some studies showed that the RR for incident diabetes is higher than it is for CVD<sup>34</sup>. Based on a meta-analysis of 42,419 participants from 16 cohorts, the average estimated RR for incident diabetes was 3.5–5.2, and did not differ appreciably with each definition. In contrast, the RR for CVD was 1.5–2.0<sup>34</sup>. The Insulin Resistance Atherosclerosis Study (IRAS) showed that the OR for diabetes development based on the NCEP and IDF definitions was similar to the WHO definition, despite the use of modified risk factors<sup>35</sup>. The study of Aboriginal Canadians showed a prevalence of diabetes three to fivefold higher than in non-Aboriginal Canadians, and metabolic syndrome had associated with incident diabetes regardless of the use of the NCEP criteria (OR 2.03; 95% CI 1.1–3.75) or IDF criteria (OR 2.14; 95% CI 1.29–3.55) to define metabolic syndrome<sup>36</sup>. In contrast, Cameron *et al.*<sup>37</sup> reported a higher OR for the WHO criteria (OR 4.6; 95% CI 3.5–6.0)

compared with EGIR criteria (OR 3.2; 95% CI 2.3–4.3), NCEP criteria (OR 3.1; 95% CI 2.3–4.0) and IDF criteria (OR 3.0; 95% CI 2.2–4.2). In addition, the OR for incident diabetes in a study of 4,756 Iranian subjects was highest using the WHO criteria (OR 11.0; 95% CI 7.9–15.3) during the 3.6-year follow-up period<sup>38</sup>. In that study, the OR using the IDF criteria was 4.3 (95% CI 3.0–6.0), the original NCEP criteria (FPG  $\geq$  110 mg/dL) was 3.7 (95% CI 2.7–5.1), and using modified NCEP criteria (FPG  $\geq$  100 mg/dL) was 4.9 (95% CI 3.5–6.9). According to a meta-analysis carried out by Ford *et al.*<sup>34</sup>, the random-effects summary RR was 5.17 (95% CI 3.99–6.69) for the WHO 1999 definition, 4.45 (95% CI 2.41–8.22) for the EGIR 1999 definition, 3.53 (95% CI 2.84–4.39) for the NCEP 2001 definition and 4.42 (95% CI 3.30–5.92) for the IDF 2005 definition.

To test which criteria enable improved predictability for the development of diabetes, we reviewed several statistical analyses that varied according to sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs) and the area under the receiver operating characteristics curve (aROC). The sensitivity ranged from 0.224 to 0.722, and the specificity ranged from 0.613 to 0.939<sup>37–43</sup>. PPVs ranged from 0.078 to 0.36 and NPVs ranged from 0.90 to 0.983<sup>37–42</sup>. A factor analysis study of 1,918 Pima Indians confirmed that the WHO definition led to superior sensitivity and specificity compared with the NCEP definition, because the former weights the presence of insulin resistance<sup>43</sup>. Also, in a longitudinal survey of 3,198 Mauritius subjects, the WHO definitions resulted in a higher value of sensitivity (42.1%) and PPV (26.8%) compared with the IDF and NCEP definitions<sup>37</sup>. However, differences among the aROCs (range 0.68–0.86) were small and insignificant, despite the differing criteria<sup>14,35,39,44–46</sup>. The predictability of metabolic syndrome for incident diabetes was superior to the predictability associated with either the Framingham Risk Score (FRS)<sup>47</sup> or classical clinical risk factors excluding laboratory parameters, such as FPG, triglyceride, HDL-cholesterol and blood pressure<sup>33</sup>.

Several studies examined that the number of metabolic syndrome components associated with the risk of type 2 diabetes<sup>16,33,47–49</sup>. According to a substudy on 3,323 members of the Framingham Heart Study Offspring Study, the RR for type 2 diabetes had increased with the number of metabolic syndrome components when the NCEP criteria were applied<sup>33</sup>. The adjusted RR for participants with three abnormalities or four more abnormalities was 4.56 (95% CI 2.48–8.78) and 10.88 (95% CI 5.77–20.50), respectively, in the British Regional Heart study<sup>47</sup>. In the West of Scotland Coronary Prevention study, Sattar *et al.*<sup>48</sup> used the NCEP definition based on body mass index (BMI) instead of waist circumference, with or without the inclusion of C-reactive protein (CRP). The estimated RR for participants with three abnormalities or four more abnormalities was 7.26 (95% CI 2.25–23.40) and 24.4 (95% CI 7.53–79.6). In the Beaver Dam study, Klein *et al.*<sup>16</sup> used a modified WHO definition to determine that the OR for the incidence of diabetes was 9.37 (95% CI 2.22–39.59) in the group

**Table 3** | Metabolic syndrome and relative risk of type 2 diabetes mellitus

References	Year	Definition	Population	n	F/U (years)	Adjusted RR or HR (95% CI)
Sattar <i>et al.</i> <sup>48</sup>	2003	Modified NCEP	West of Scotland Coronary Prevention Study (male adults)	5,974	4.9	7.26 (2.25–23.4) in 3 components 24.4 (7.53–79.6) in 4 components 7.65 (5.99–9.31) in IFG components
Wilson <i>et al.</i> <sup>33</sup>	2005	NCEP	Framingham Offspring study (middle-aged adults)	3,323	8.0	11.0 (8.1–14.9) in metabolic syndrome including IFG 5.0 (3.7–6.8) in metabolic syndrome excluding IFG
Wang <i>et al.</i> <sup>72</sup>	2007	WHO EGIR AACE IDF Modified NCEP	Beijing Project (part of the National Diabetes Survey Population)	541	5.0	2.39 (1.51–3.77) 1.88 (1.08–3.27) 2.97 (1.85–4.76) 2.05 (1.27–3.30) 2.33 (1.47–3.70) 2.61 (1.61–4.24) in IFG component
Cheung <i>et al.</i> <sup>40</sup>	2007	Modified NCEP IDF	Hong Kong Cardiovascular Risk Factor Prevalence Study cohort	1,679	6.4	4.1 (2.8–6.0) 3.5 (2.3–5.2) 5.1 (3.0–8.7) in IFG components
Cameron <i>et al.</i> <sup>37</sup>	2007	WHO EGIR NCEP IDF	A longitudinal survey in Mauritius	3,685	5.0	4.6 (3.5–6.0) 3.2 (2.3–4.3) 3.1 (2.3–4.0) 3.0 (2.2–4.2) 3.3 (2.6–4.3) in IFG component
Cameron <i>et al.</i> <sup>42</sup>	2008	WHO EGIR IDF NCEP	Australian Diabetes, Obesity, and Lifestyle (AusDiab) study (adults, age $\geq 25$ years)	5,842	5.0	7.8 (5.5–11.0) 7.4 (5.2–10.4) 5.5 (3.9–7.6) 6.4 (4.6–9.0) 3.05 in IFG component
Ley <i>et al.</i> <sup>36</sup>	2009	NCEP IDF	Sandy Lake Health and Diabetes Project	492	10	2.03 (1.10–3.75) 2.14 (1.29–3.55) 2.30 (1.40–3.77) per 1 mmol/L increment of FPG
Salminen <i>et al.</i> <sup>51</sup>	2012	IDF	Populations of Lieto in Finland (age $\geq 64$ years)	1,117	9	3.15 (1.89–5.25) 5.16 (2.68–9.93) in IFG component

CI, confidence interval; EGIR, European Group for the Study of Insulin Resistance; F/U, follow-up period; FPG, fasting plasma glucose; HR, hazard ratio; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; NHANES, National Health and Nutrition Examination Survey; RR, relative risks; WHO, World Health Organization.

with three abnormalities and 33.67 (95% CI 7.93–142.96) in the group with four or more abnormalities. Another study that was not based on one of the major definitions also reported that the RR relates to three or more risk factors<sup>49</sup>.

Among the components of metabolic syndrome, IFG has been shown as the strongest predictor for type 2 diabetes development<sup>37,40–42,50</sup>. Subjects with metabolic syndrome, which included the IFG trait, showed a RR of 11.0 (95% CI 8.1–14.9), whereas the RR for subjects excluding IFG were 5.0 (95% CI 3.7–6.8) in the Framingham Offspring Study<sup>33</sup>. Lorenzo *et al.*<sup>41</sup> showed that the OR of incidental diabetes was 5.03 (95% CI 3.39–7.48) in participants with metabolic syndrome excluding IFG, 7.07 (95% CI 3.32–15.1) in participants without metabolic syndrome including IFG, and 21.0 (95% CI 13.1–33.8) in participants with metabolic syndrome including IFG when the

NCEP criteria were used. The trend is also similar to the IDF definition (4.51 [95% CI 3.05–6.68] vs 10.5 [95% CI 5.50–24.3] vs 21.5 [95% CI 13.3–34.8]). In a recently published study on older populations in Finland, the HR of each metabolic syndrome component for the development of type 2 diabetes was 1.75 (95% CI 1.04–2.95) for the obesity factor, 1.34 (95% CI 0.78–2.31) for the triglyceride factor, 1.60 (95% CI 0.91–2.81) for the HDL-cholesterol factor, 1.87 (95% CI 0.45–7.76) for the blood pressure factor and 5.16 (95% CI 2.68–9.93) for the IFG factor<sup>51</sup>. The strong relationship between metabolic syndrome with IFG and incident type 2 diabetes mellitus was not predictive of CVD. Whether other components (except for FPG) are related to incident diabetes remains controversial. Hwang *et al.*<sup>31</sup> reported that a dramatic decrease in the risk of incident diabetes was observed in men after the initial FPG was

adjusted, and metabolic syndrome without IFG was not associated with incident diabetes in women. However, the individual components of metabolic syndrome associated independently with risk for incident diabetes. As aforementioned, metabolic syndrome without IFG associated significantly with risk for incident diabetes; however, the RR in this case was less than the RR in metabolic syndrome with IFG.

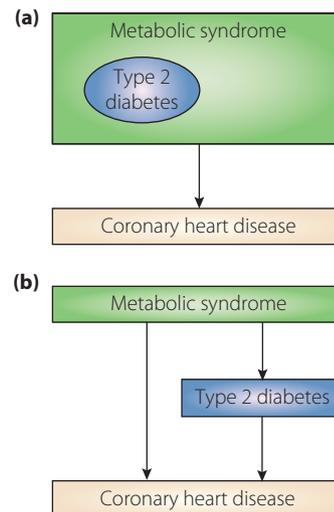
A few studies have shown that the incorporation of some markers not of traditional metabolic syndrome components can be used as new metabolic syndrome components. In the European Investigation into Cancer and Nutrition (EPIC)-NL, Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) study, the predictive ability of type 2 diabetes in the extended model with high sensitivity of CRP (hsCRP) was slightly better than the predictive ability of the standard model of metabolic syndrome<sup>52</sup>. Furthermore, several studies have considered additional features, such as markers of liver function, uric acid and albumin<sup>20,53,54</sup>. However, more research is required to confirm the validity of these new markers.

### CLINICAL INTERPRETATIONS OF METABOLIC SYNDROME

Some concern has emerged with regard to the lack of certainty inherent to metabolic syndrome, its pathogenesis and its value as a risk marker of CVD<sup>13</sup>. Nevertheless, the syndrome is used widely and conveniently in clinical practice and research fields; an important aspect of its clinical significance is the ‘visualization’ of the risk for CVD and type 2 diabetes development. By receiving a diagnosis of metabolic syndrome, patients might become motivated to actively carry out lifestyle modifications, and physicians can implement the focused risk management and comprehensive implementation approaches available to them to mitigate major complications.

The debate has continued on the inclusion of type 2 diabetes mellitus in definitions of metabolic syndrome (Figure 1)<sup>55</sup>. Early detection of individuals at high risk for type 2 diabetes is essential not only for the prevention of diabetes itself, but also to decrease associated cardiovascular complications. As aforementioned, metabolic syndrome is ideal as a predictor of incident diabetes. With the inclusion of diabetes in the defining criteria, metabolic syndrome loses its clinical advantage as a predictor for the development of diabetes. In addition, physicians should not expect effects from concurrent prevention measures for incident type 2 diabetes and its complications to overlap with active intervention of metabolic syndrome. Therefore, heavy consideration should be given to the exclusion of diabetes from the definition, and more focus should fall on the role of metabolic syndrome as an intervention tool for diabetes prevention.

Among the five components of metabolic syndrome, IFG is particularly superior for its ability to predict incident diabetes<sup>33,41,51</sup>; the other components can predict CVD better than or similarly to IFG<sup>33</sup>. Thus, metabolic syndrome with IFG is complimentary, allowing the prediction of CVD and diabetes; the populations in this group require extra care in management.



**Figure 1** | Concept of metabolic syndrome according to its major clinical outcome. (a) Classical concept of metabolic syndrome including type 2 diabetes as one of the main components. (b) Proposed concept that type 2 diabetes mellitus is regarded as a major outcome of metabolic syndrome.

The role of metabolic syndrome in patients who have been diagnosed with diabetes is a topic many believe should not be ignored. Alexander *et al.*<sup>55</sup> reported that in the USA, over 80% of participants aged 50 years or older with diabetes also have metabolic syndrome. Most patients with type 2 diabetes possess multiple risk factors for CVD other than hyperglycemia. Because CVD is the leading cause of death in diabetic patients<sup>56,57</sup>, careful attention should be exercised with regard to all modifiable risk factors. Many clinical studies have confirmed that adequate control of blood pressure and lipid profiles can reduce cardiovascular risk effectively<sup>58–60</sup>. However, diabetes itself is a strong risk factor for CVD, and type 2 diabetes mellitus is well-known for its similar risks to coronary heart disease<sup>61</sup>. Consequently, the value of metabolic syndrome in diabetic patients is relatively weak compared with its value in non-diabetic subjects.

In conclusion, metabolic syndrome is immensely useful as a clinical tool to predict diabetes and CVD, especially in high-risk groups with metabolic syndrome that includes IFG. Exclusion of diabetes mellitus in metabolic syndrome is important to maximize the prevention effect of CVD with preceding diabetes mellitus. Further studies are required in several areas, including unified classification, ambiguous pathogenesis, the ‘syndrome’ role and the development of a more effective model.

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