Metabolic Syndrome and Incidence of Stroke

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Abstract: The relationship between metabolic syndrome and stroke has not been investigated <u>as</u> widely as that for coronary heart disease. The aim of the study is to make an overall review of the published articles on metabolic syndrome and the stroke incidence. Eight population-based prospective studies are included and a meta-analysis based on the published data was performed. The combined overall hazard ratio for stroke incidence was similar (around 1.7) for different definitions of the metabolic syndrome. A European study which has compared four different definitions using paired homogeneity test did not find any difference in the prediction of the ischemic stroke incidence and there was also no differences between a full definition and its single individual components.

INTRODUCTION

Since 1998 many different definitions for the metabolic syndrome have been introduced. The World Health Organization (WHO) was the first to introduce a provisional definition for the metabolic syndrome in 1998 [1] and this was revised in the 1999 [2]. The WHO includes in its definition the insulin resistance under hyperinsulinemic and euglycemic conditions, and microalbuminuria [2]. The European Group for Study of Insulin Resistance (EGIR) introduced a simple definition based on the WHO one in 1999, in which the insulin resistance was defined using the top quartile distribution of fasting insulin concentration among the non-diabetic individuals of the background population and waist circumference was used to replace the body mass index (BMI) and waist to hip ratio (WHR) [3]. In 2001, the National Cholesterol Education Program Adult Treatment Expert Panel III (NCEP_2001) approved a new definition based on five components and any three abnormalities of the five forms a definition [4, 5]. Insulin resistance was not included in the NCEP definition. The NCEP_2001 definition was further modified in 2004 (NCEP_2004) [6], in which the fasting plasma glucose (FPG) cut-off value was lowered from 6.1 mmol/l to 5.6 mmol/l. The American Association of Clinical Endocrinologists (AACE) made a clinical definition in 2003 [7, 8]. The latest major definition came from the International Diabetes Federation (IDF). The IDF consensus group approved their definition in 2005 to emphasize the importance of central obesity [9, 10]. The major components of these definitions are more or less similar but with different emphasis (Table **1**).

The prevalence of the metabolic syndrome varies depending on the definitions used even in the same study population [11, 12]. A great surge of publications has been created to compare the differences of these definitions with regard to their prevalence and their prediction of cardiovascular disease (CVD) and diabetes. Based on the published data, several meta-analyses were carried out and published. These data have unequivocally shown that the metabolic syndrome of different definitions all increased the risk of CVD [12-15] and diabetes [16, 17], but the prediction was stronger for diabetes than for CVD. A few studies have, however, challenged the definition of the metabolic syndrome by showing that the individual metabolic component predicted the CVD by a similar magnitude as that of the full definition of the syndrome [18-20], and fasting glucose alone was a stronger risk predictor for the future diabetes than was the full definition of the metabolic syndrome. In this article relationship between metabolic syndrome of different definitions and the incidence of stroke was quantitatively reviewed.

DATA SOURCES AND LIMITATIONS

Publications in English language from 1975 onwards on metabolic syndrome and stroke were searched from PubMed using title terms "metabolic syndrome" and "stroke". Prospective studies with population-based cohort design that have estimated the hazard ratio of the metabolic syndrome for predicting stroke were eligible for the current review, and summarized in Table **2**. Eight studies were included which consisted of limited ethnic groups: American white&black in two studies (one in middle-aged and another in elderly population)[21, 22], Finnish in two (one in middle-aged men and another in elderly men and women)[23, 24], Japanese in two (middle-aged)[25, 26], and Chinese in one study (middle-aged)[27]. A meta-analysis based on individual data of Finnish and Swedish populations was also included [28]. Multivariate adjusted hazard ratios were reported in the Table **2** if more than two hazard ratios have been presented in one article. As shown in the Table **2** the adjustment varies among studies. Three of the eight studies have estimated the ischemic stroke, four with all stroke and one did not mention the type of the stroke. Different definitions of the metabolic syndrome have been applied and indicated in the Table **2**.

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Table 1.   Major Definition of the Metabolic Syndrome of Different Organizations

	WHO	NCEP_2001	NCEP_2004	IDF
Insulin resistance	Hyperinsulinemic and euglycemic*			
2h plasma glucose (mmol/l)	≥7.8*			
Fasting plasma glucose((mmol/l)	≥6.1*	≥6.1	≥5.6	≥5.6
Blood pressure (mmHg)	≥140/90	≥130/85	≥130/85	≥130/85
Triglyceride (mmol/l)	≥1.7 and/or	≥1.7	≥1.7	≥1.7
HDL-cholesterol (mmol/l)	<0.9 (1.0)	<1.03 (<1.29)	<1.03 (<1.29)	<1.03 (<1.29)
Waist circumference (cm)		>102 (>88)	>102 (>88)	≥94 (≥80)*
WHR/BMI (kg/m2)	>0.9 (0.85)/>30			
Albuminuria	≥20μg/min			
Definition	*Prerequisite+ any two of the others	Any three	Any three	*Prerequisite + any two of the others

Previously diagnosed diabetes or those taking anti-hypertensive treatment are counted in all four definitions.
*Prerequisite.

DATA ANALYSIS

Multivariate adjusted hazard ratios (95% CI) for stroke attributed to metabolic syndrome of different definitions was collected from each study, and combined into an overall hazard ratio by a fixed-effects approach according to the method detailed by Fleiss [29], the combined overall hazard ratio as well as individual hazard ratios are shown in Fig. (**1a-c**).

RESULTS

The hazard ratios corresponding to different definitions varied slightly among studies and even within a study, but the overall hazard ratios calculated based on the meta-analysis of all studies were, however, similar around 1.7 (Fig. **1a-c**) for all definitions studied.

In the meta-analysis of 6 Finnish and Swedish cohorts of 4038 men and 3813 women of 25-74 years old, the risk size of different definitions as well as their individual components has been compared using paired homogeneity test [28]. During follow-up of 4 to 12 years, 113 incident ischemic stroke events in men and 47 in women were accumulated. The hazard ratio for each of the full definitions of the metabolic syndrome was presented in the Table **2**, they were not statistically significantly different from each other [28]. The hazard ratios for ischemic stroke in men were 2.09 (1.39-3.14) and 1.86 (1.17-2.98) for FPG of 6.1-6.9 mmol/l and for elevated blood pressure of ≥140/90 mmHg or treated, and 3.21 (1.61-6.39) and 2.61 (1.24-5.50) in women, respectively. When a full definition of the metabolic syndrome was compared with its single components the study did not find that a full definition was superior to its single components with regard to the prediction of the ischemic stroke. None of the four definitions of the metabolic syndrome or its single components predicted hemorrhagic stroke except for the elevated blood pressure, hazard ratios of 2.78 (1.21-6.39) in men and 8.30 (2.11-32.63) in women for blood pressure of 140/90 mmHg or treated [28]. The study concluded that metabolic syndrome as well as its individual components predicted the incidence ischemic stroke equally well and should be treated equally as well.

CONCLUSIONS

Regardless of the differences in definitions of the metabolic syndrome, the risk sizes for stroke are similar (hazard ratio of 1.7) among different definitions, which was lower than those reported for the incidence of type 2 diabetes (hazard ratios of 3.5 to 5.1) [16]. This is because the components included in these definitions are more or less similar, and the component that appears most frequently among all others is the elevated blood pressure. Elevated blood pressure is alone a strong risk factor for either ischemic or hemorrhagic stroke, and the risk size is similar to those of its full definitions [28]. A cluster of elevated blood pressure with others seems do not further increase the risk of stroke. It has been shown that type 2 diabetes clustering with hypertension was more strongly associated with the concurrence of cardiovascular events than other clusters of the metabolic syndrome among type 2 diabetic patients [30].

There are many different ways to diagnose a metabolic syndrome. This creates different traits of individuals identified as having the syndrome, some with high CVD risk but others low risk [30]. Because the inter-individual heterogeneity, the syndrome can not be considered as a single disease entity. Currently there is no a single treatment targeting at the syndrome rather than at each of its single components. From a clinical as well as a public health point of view, to increase the awareness of the clustering of certain metabolic disorders among doctors and public may help to identify people with multiple risk factors and lead to a poly pills treatment to prevent further progress to more serious clinical end points. The causes underlying the clustering and its pathophysiological changes require further researches. The relationship of metabolic syndrome with subtypes of stroke rather than ischemic stroke may need further clarification.

Table 2. **Hazard Ratio (95%CI) of Stroke Incidence in Relation to the Presence of Metabolic Syndrome at Baseline in Studies of Population-Based**

Studies	Age (Year)	No.	Follow-Up (Year)	Stroke Type Number	Definition	Hazard Ratio	Adjustment and Comment
McNeill (2005) American white & black	45-64	Men5208 Women 6881	11 (mean)	Ischemic Men 123 Women 93	NCEP_2001 NCEP_2004	Men 1.42 (0.96-2.11) Women 1.96 (1.28-3.00) Men 1.52 (1.05-2.18) Women 1.90 (1.25-2.89)	Age, race, study center, LDL cholesterol, smoking. In non-diabetics.
McNeill (2006) American white &black	≥65	Men 1356 Women 2229	11 (median)	Ischemic and hemorrhagic Men 146 Women 255	NCEP_2004	Men 1.51 (1.08-2.12) Women 0.94 (0.73-1.21)	Age and race. In non-diabetics.
Kurl 2006 Finnish men	42-60	Men 1131	14 (mean)	Men 65	NCEP_2004 WHO modified	All 2.39 (1.17-4.89) Ischemic 2.78 (1.24-6.23) All 2.08 (1.12-3.87) Ischemic 2.47 (1.21-5.07)	Age, examination year, Socioeconomic status, smoking, alcohol, family history of heart disease, ischemic changes during exercise test, LDL cholesterol, energy intake for saturated fats, energy expenditure of leisure time physical activity, blood leukocyte count, and plasma fibrinogen In non-diabetics.
Iso 2007 Japanese	40-69	Men 3595 Women 5492	18	Ischemic Men 144 Women 112	NCEP_2001, but replacing waist with BMI≥25 kg/m^2	Men 2.0 (1.3-3.1) Women 1.5 (1.0-2.3)	Age, sex, community, TC, smoking, alcohol, and menopause for women only. Including diabetics.
Liu 2007 Chinese	35-64	Men + women 30378	10	Iscehmic& hemorrhagic # not available	NCEP_2004, but using waist≥ 90 (80)cm	Ischemic 2.41 (1.98-2.94) hemorrhagic 1.63 (1.16-2.30)	Age, sex, smoking, CVD family history, and TC Including diabetics.
Ninomiya 2007 Japanese	≥40	Men 1050 Women 1402	14	All stroke Men 94 Women 115	NCEP_2001, but waist≥ 90 (80)cm	Men 1.92 (1.23-2.98) Women 1.50 (1.03-2.19)	Age, proteinuria, electrocardiogram abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise. Including diabetics.
Wang 2008 Finnish	65-74	Men+Women 991	14	All stroke 137	NCEP_2001 NCEP_2004 WHO IDF	1.60 (1.14-2.25) 1.49 (1.06-2.10) 1.57 (1.12-2.19) 1.77 (1.24-2.54)	Age, Sex. In non-diabetics.
Qiao 2008 European	25-74	Men 4038 Women 3813	4-21	Ischemic & Hemorrhagic Men 167 Women 63	Ischemic stroke NCEP_2001 NCEP_2004 WHO_modified IDF	Men 1.52 (1.01-2.28) Women 2.68 (1.47-4.87) Men 1.16 (0.77-1.74) Women 2.31 (1.27-4.20) Men 1.59 (1.09-2.32) Women 2.20 (1.15-4.19) Men 1.27 (0.87-1.86) Women 1.91 (1.05-3.49)	Age as time scale, adjusting for cohort, smoking, and total cholesterol In individuals without a prior history of diabetes No relationship was found for hemorrhagic stroke.

ABBREVIATIONS

WHO = World Health Organization

EGIR = The European Group for Study of Insulin Resistance

NCEP = The National Cholesterol Education Program Adult Treatment Expert Panel

IDF = The International Diabetes Federation

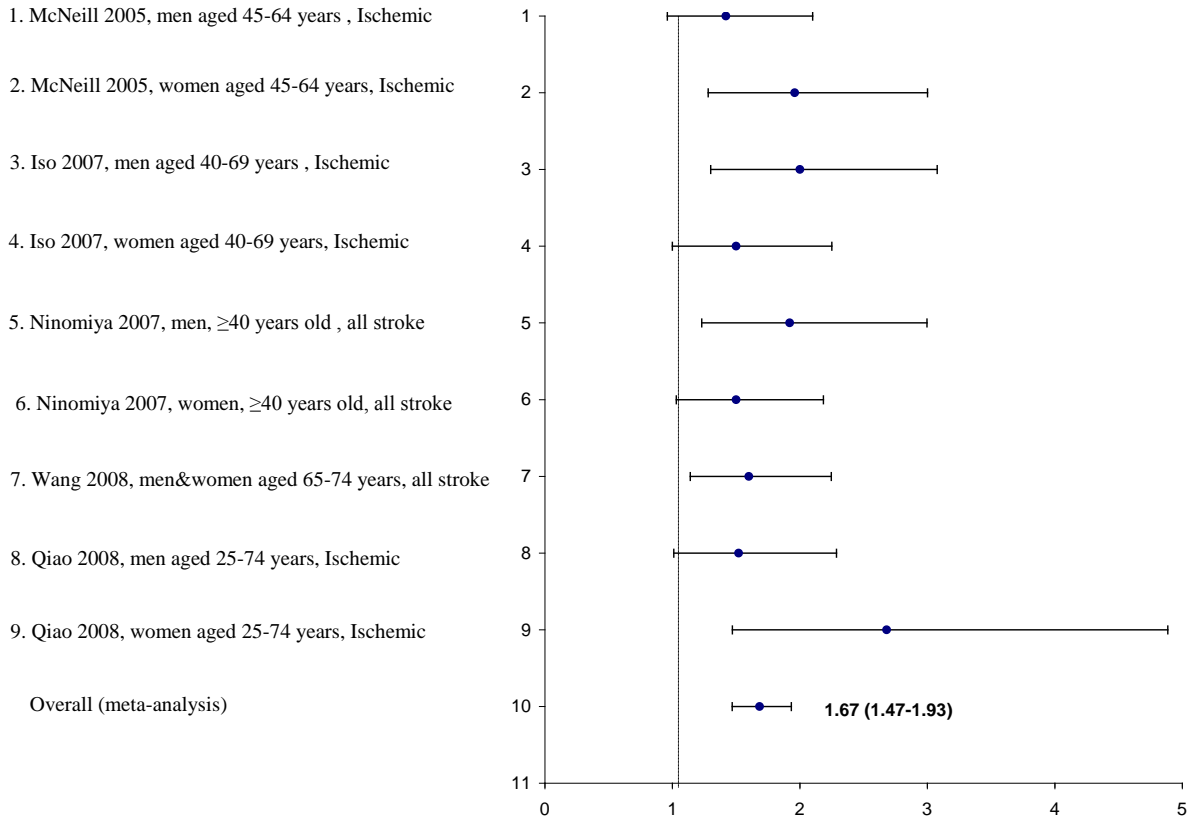AACE = The American Association of Clinical Endocrinologists

BMI = Body mass index

WHR = Waist to hip ratio
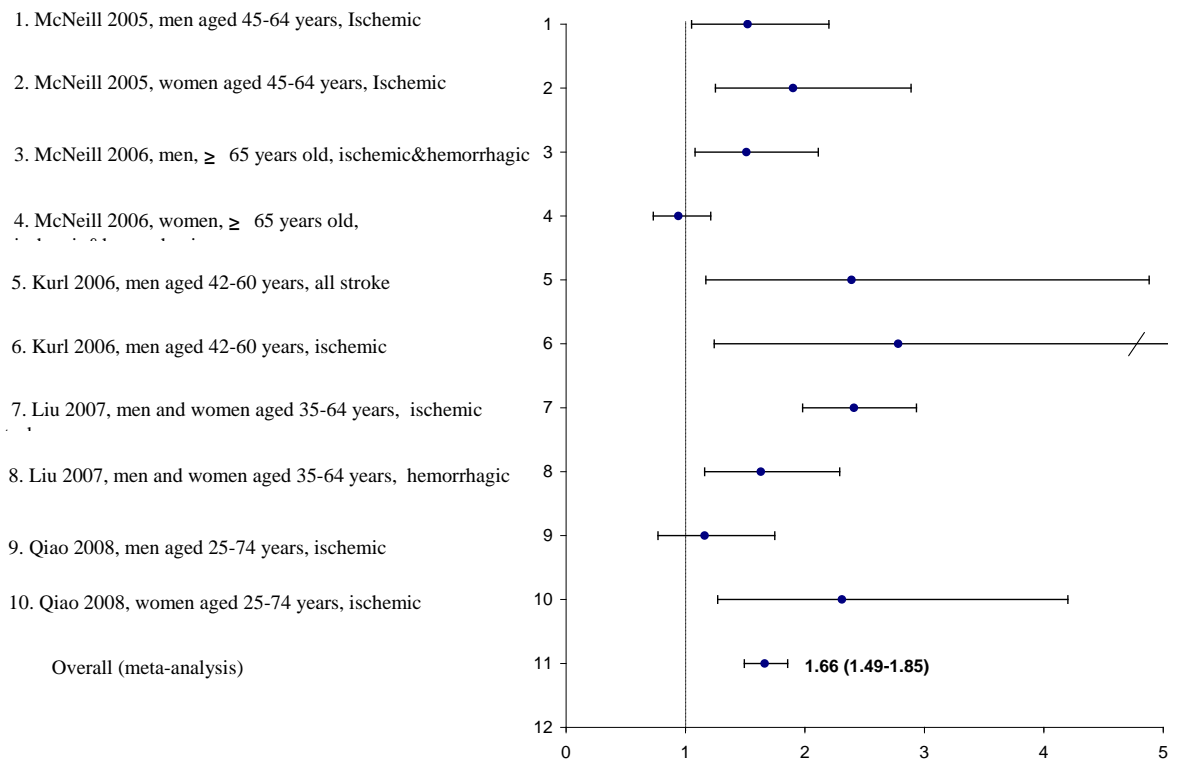
CVD = Cardiovascular disease

FPG = Fasting plasma glucose

(a)

1. McNeill 2005, men aged 45-64 years , Ischemic

2. McNeill 2005, women aged 45-64 years, Ischemic

3. Iso 2007, men aged 40-69 years , Ischemic

4. Iso 2007, women aged 40-69 years, Ischemic

5. Ninomiya 2007, men, ≥40 years old , all stroke

6. Ninomiya 2007, women, ≥40 years old, all stroke

7. Wang 2008, men&women aged 65-74 years, all stroke

8. Qiao 2008, men aged 25-74 years, Ischemic

9. Qiao 2008, women aged 25-74 years, Ischemic

Overall (meta-analysis)   **1.67 (1.47-1.93)**

Relative risk (95%CI) for stroke incidence, using NCEP 2001 definition

(b)

1. McNeill 2005, men aged 45-64 years, Ischemic

2. McNeill 2005, women aged 45-64 years, Ischemic

3. McNeill 2006, men, ≥ 65 years old, ischemic&hemorrhagic

4. McNeill 2006, women, ≥ 65 years old,

5. Kurl 2006, men aged 42-60 years, all stroke

6. Kurl 2006, men aged 42-60 years, ischemic

7. Liu 2007, men and women aged 35-64 years, ischemic

8. Liu 2007, men and women aged 35-64 years, hemorrhagic

9. Qiao 2008, men aged 25-74 years, ischemic

10. Qiao 2008, women aged 25-74 years, ischemic

Overall (meta-analysis)   **1.66 (1.49-1.85)**

Relative risk (95%CI) for stroke incidence, using NCEP 2004 definition

(c)

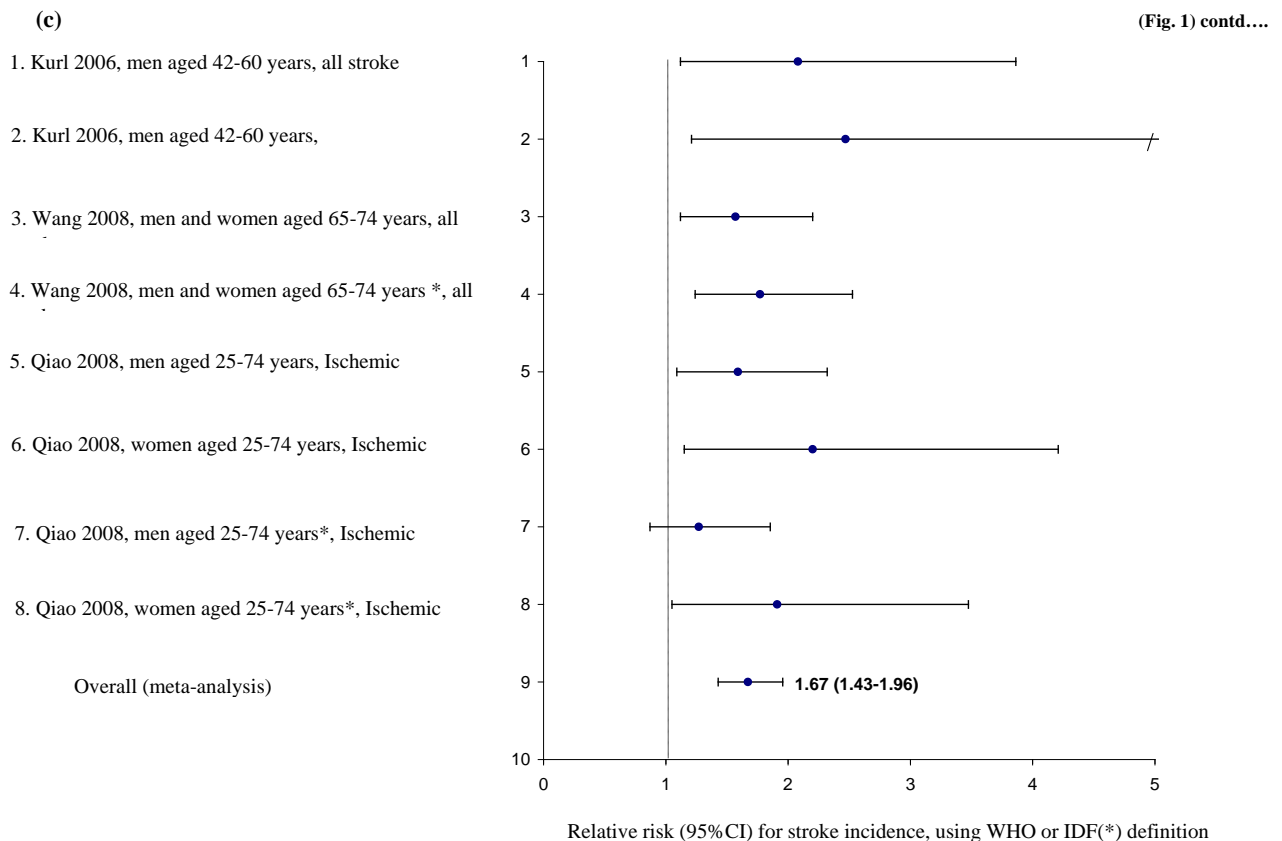Relative risk (95%CI) for stroke incidence, using WHO or IDF(*) definition

Fig. (1). Meta-analysis of the effect of metabolic syndrome on stroke incidence using the NCEP_2001 (**a**) NCEP_2004 (**b**) and the WHO/IDF definition (**c**).

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