Table 1—*Characteristics of studies included in meta-analysis*

First author	Year	Cohort designation	Population	Follow-up (years)	Diabetes ascertainment*	Baseline SUA (mg/dl)	Age (years)	% Men	Number of participants†	Number of cases	Cohort design
Medalie (15)	1975	IIHDS	Israel	5.0	Both	4.8	49	100	8,688	344	H
Ohlson (16)	1988	SMB	Sweden	13.5	Both	5.3	50	100	766	47	H
Perry (17)	1995	BRHS	British	12.8	Report	6.0	50	100	7,577	194	P
Chou (18)	1998	KS	China	2.0	Measure	5.8	50	52	654	39	H
Taniguchi (19)	2001	OHS	Japan	9.5	Measure	5.2	41	100	6,478	639	P
Meisinger (20)	2002	MONIKA	Germany								
Men				7.6	Report	5.7	52	100	3,052	128	H
Women						4.0	51	0	3,114	85	H
Lin (21)	2004	KS	China	7.0	Both						
Men						8.0	49	100	293	27	H
Women						7.1	55	0	161	21	H
Chien (22)	2008	CSCCC	China	9.0	Measure	5.6	54	43	2,690	548	H
Dehghan (23)	2008	RS	the Netherlands	10.1	Both	5.4	over 55	NA	4,536	462	P
Nan (24)	2008	MNCDS	Mauritius	8.2	Both						
Men						6.6	41	100	1,941	337	H
Women						5.0	42	0	2,318	379	H
Kramer (25)	2009	UC	U.S.	13.0	Measure	5.7	63	41	566	55	H

*Measure = using blood measurements, report = using reports by participants or physicians, and both = using both blood measurements and reports by participants or physicians. †Number of participants included in the analysis in each study (not necessarily the number of participants at the beginning of each study). BRHS, British Regional Heart Study; CSCCC, Chin-Shan Community Cardiovascular Center; H, historical cohort; IIHDS, Israel Ischemic Heart Disease Study; JAPF, Japan Arteriosclerosis Prevention Fund; KS, The Kinmen Study; MNCDS, Mauritius Non-Communicable Diseases Surveys; MONIKA, MONIKA-Augsberg Cohort Study; NA, not available; OHS, The Osaka Health Study; P, prospective cohort; RS, The Rotterdam Study; SMB, The Study of Men Born in 1913; UC, University of California.

If a study provided several RRs, such as unadjusted and adjusted RRs, the most completely adjusted RR was used. Each RR was transformed to its natural logarithm (log RR), and its corresponding 95% CI or *P* value was used to calculate the SE for each log RR. Two of our investigators independently reviewed each published article and extracted the relevant information. Any disagreement was resolved by consensus.

Data synthesis

To quantify the dose-response relationship between the baseline SUA level and risk of type 2 diabetes, we calculated the RR for each 1 mg/dl increase in SUA in each study. For studies that analyzed SUA level not as a continuous but as a categorical variable (i.e., studies where subjects were categorized based on SUA level and RRs for the development of type 2 diabetes according to SUA level were reported), we used the method for trend estimation supported by Berlin et al. (6) and Orsini et al. (7). This method is particularly useful when the full data are not available. It enables us to correct for covariance between risk estimates from the same study and to estimate the corrected linear trend using generalized least squares if data on the adjusted RR and the number of participants (or person-time) and cases for each category are provided.

When the mean SUA level was not reported, the range's midpoint in each category was used, except for the lowest and highest category, for which the mean SUA level was estimated by assuming normality of SUA distribution, which is the same method as used in a previously published meta-analysis (8). Each log RR was pooled by using a random-effects model (9). The overall RR and its 95% CI could be calculated by exponentiation of the pooled log RR. We assessed heterogeneity of RRs across studies using both I^2 and Q statistics (10).

Sensitivity analyses

The studies included were stratified by key factors related to cohort design (i.e., prospective or historical cohort) and other study properties related to study quality and participant characteristics that were identified a priori. Study quality was assessed according to the method of ascertainment of diabetes (whether blood measurements, or reports by participants or physicians, or both), mean follow-up duration (>8 or ≤8 years), and inclusion of adjustment for the following potentially important confounding variables: alcohol intake (yes or no) and metabolic profile (sufficient or insufficient). We regarded the adjustment for metabolic variables as sufficient when the risk estimate was adjusted for more than three factors among obesity, hypertension (or systolic blood pressure), fasting plasma glucose, HDL cholesterol, and triglycerides. We identified country of origin (Asian or Western countries), mean age (>50 or ≤50 years), sex (whether men only, women only, or both men and women), and mean SUA level (>5.5 or ≤5.5 mg/dl) as possible participant characteristics. We calculated the pooled RR within the strata of each study characteristic, and meta-regression analyses were conducted to assess the effects of these study characteristics on the type 2 diabetes risk and incremental increase in SUA level.

The possibility of publication bias was assessed by the Begg's and the Egger's tests (11,12) and visual inspection of a funnel plot. We also performed the Duval and Tweedie "trim-and-fill" procedure (13) to further assess the possible effect of publication bias in our meta-analysis. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they actually existed. Data were analyzed by

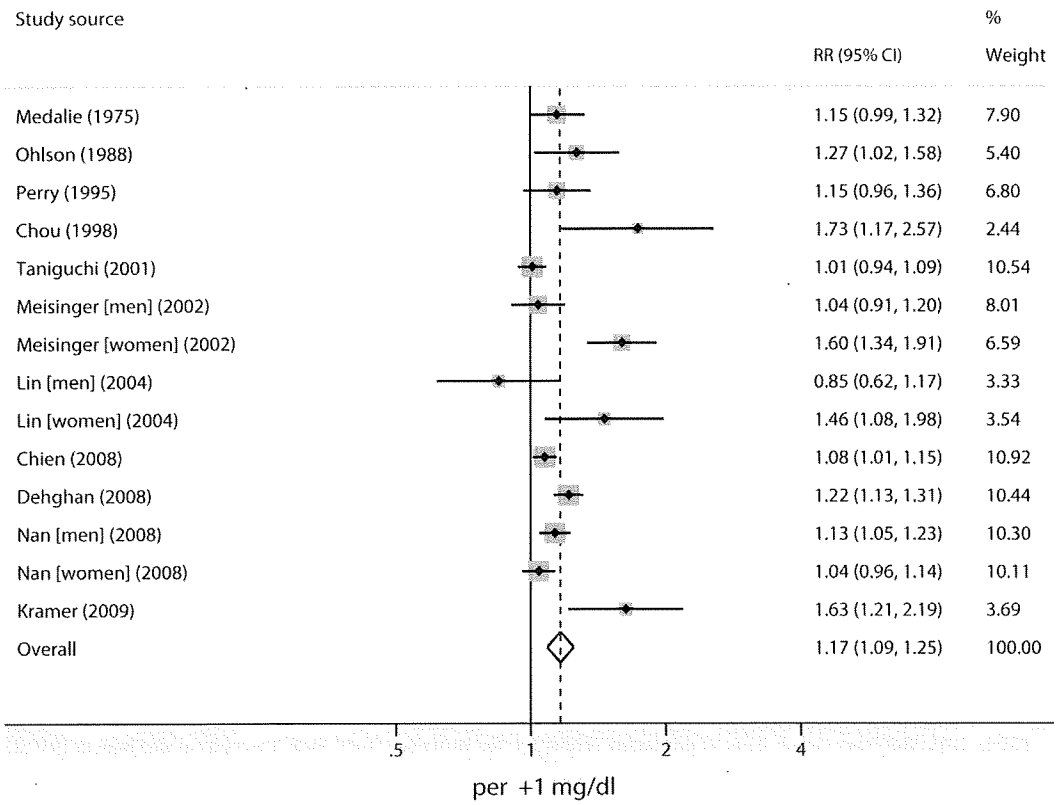

Figure 1—*Overall RR (with corresponding 95% CIs) for risk of type 2 diabetes for each mg/dl increase in SUA. The area of each square is proportional to study weight. Diamond indicates overall RR; horizontal lines indicate 95% CIs.*

using STATA software (version 10; Stata, College Station, TX). $P < 0.05$ was considered as statistically significant except for the test of publication bias, in which the level of significance is $P < 0.10$ (14).

RESULTS

Literature search

Of 1,258 citations retrieved by the search strategy, 1,225 citations were excluded after a first screening based on titles and abstracts, leaving 33 articles for full-text review. Manual searching of the reference lists of these articles identified 8 additional articles. Of 41 articles for full-text review, 30 articles were excluded for the following reasons: *1*) they were case-control studies (6 studies); 2) they were clinical trials (3 studies); 3) risk estimates of the association of type 2 diabetes with SUA level were not reported (9 studies); *4*) prespecified outcome did not include type 2 diabetes (5 studies), and sufficient data to estimate the RR of type 2 diabetes and its corresponding SE per incremental increase in UA were not provided (4 studies); and 5) data reported were updated by more recent studies (3 studies). Eleven studies (15–25) met the inclusion criteria. Three studies investigated men and women separately. Finally, 14 cohorts involving a total of 42,834 participants and 3,305 incident cases were included in our analyses.

Study characteristics

Characteristics of the 11 included studies are shown in Table 1. Three studies (17,19,23) were prospective cohort and eight studies (15,16,18,20–22,24,25) were historical cohort. The selected studies were published between 1975 and 2009, and the number of subjects per study ranged from 250 to 8,688. Mean SUA level of subjects ranged from 4.0 to 8.0 mg/dl, and mean age ranged from 41 to 63 years except for one study (23), in which data on mean age (>55 years) were not available. Four studies (15–17,19) included men only, and seven studies (18–21,23–25) included both women and men. Six studies (15,18,19,21,22,24) were conducted in Asian countries and five studies (16,17,20,23,25) in Western countries. Mean follow-up duration ranged from 2.0 to 13.5 years.

Regarding methods for ascertaining diabetes, four studies (18,19,22,25) used blood measurements only, two (17,20) used reports by participants and/or physicians only, and five (15,16,21,23,24) used both. Risk measures were adjusted for alcohol intake in five studies (17,19,20,22,24), and the adjustment for sufficient metabolic variables was sufficient in five studies (18,21–24). A few risk estimates were adjusted for smoking status (three studies) (17,19,20), family history of diabetes (four studies) (16,20,22,24), and fasting insulin concentration (three studies) (18,21,24). Only two studies (21,24) considered the effect of serum creatinine, and one study (25) considered the effect of diuretic use. None of risk measurements was adjusted for other drugs that influence SUA level such as alloprinol.

Overall and stratified analyses

Figure 1 shows a forest plot with RRs and 95% CIs and pooled estimates for the reduction in risk of type 2 diabetes for each

Table 2—*Stratified and meta-regression analysis to explore the effects of study characteristics*

	Number of cohorts	Pooled RRs (95% CI)*	*P* value of meta-regression†
Study design			
Historical cohort	10	1.22 (1.10–1.36)	0.55
Prospective cohort	4	1.10 (1.01–1.20)	
Indicators of participant characteristics			
Country			
Asia	8	1.09 (1.04–1.21)	0.10
Western	6	1.27 (1.12–1.44)	
Mean age (years)			
≤50	8	1.12 (1.04–1.19)	0.14
>50	6	1.26 (1.11–1.44)	
Sex			
Men only	7	1.09 (1.02–1.16)	0.09
Women only	4	1.28 (1.08–1.51)	0.31
Both men and women	3	1.40 (0.98–2.00)	
Mean SUA level (mg/dl)			
≤5.5	6	1.18 (1.15–1.32)	0.98
>5.5	8	1.16 (1.05–1.28)	
Indicators of study quality			
Study adjustment for alcohol intake			
No	9	1.27 (1.13–1.43)	0.02
Yes	5	1.07 (1.02–1.12)	
Metabolic confounders‡			
Insufficient	8	1.21 (1.09–1.34)	0.46
Sufficient	6	1.11 (1.02–1.21)	
Follow-up duration (years)			
≤8	6	1.25 (1.03–1.51)	0.37
>8	8	1.13 (1.05–1.20)	
Diabetes ascertainment			
Blood measurements only	4	1.18 (1.02–1.37)	0.81
Report only	3	1.24 (0.96–1.59)	0.64
Both	7	1.14 (1.06–1.23)	

*Pooled RRs of type 2 diabetes for each 1 mg/dl increase in SUA within the strata of each study characteristic are indicated. †Represents the test for significance of the effect across strata. ‡If the RRs were adjusted for more than three confounders (among BMI, fasting plasma glucose, hypertension [or systolic blood pressure], HDL cholesterol, and triglycerides), they were regarded as sufficient; otherwise, they were regarded as insufficient.

mg/dl increase in SUA. The pooled crude RR (95% CI) was 1.17 (1.19–1.25). There was evidence of statistical heterogeneity of RRs across studies (*Q* statistic, 50.4; I^2 statistic, 74.2%; $P < 0.001$).

Table 2 shows findings of the stratified and meta-regression analysis to explore the effects of study characteristic. An increased risk of type 2 diabetes associated with an incremental increase in SUA was consistently found within all strata of each study characteristic (i.e., all pooled RRs were >1). There were no significant differences in the pooled risk estimates between cohort design (pooled RR [95% CI] of 1.22 [1.10–1.36] for historical cohort and 1.10 [1.01–1.20] for prospective cohort, $P = 0.36$). The influence of participant characteristics on the study results was not significant. Adjustment for alcohol intake attenuated the association between SUA and type 2 diabetes risk ($P = 0.02$), whereas the effect of sufficient adjustment for metabolic variables was not significant ($P = 0.46$).

Test of publication bias

Visual inspection of the funnel plot revealed asymmetry (see online appendix A [available at http://care.diabetesjournals.org/cgi/content/full/dc09-0288/DC1]). This raises the possibility of publication bias, which was statistically supported by the Egger's test ($P = 0.06$). We decided to adjust for this publication bias using the trim-and-fill method (13). According to this method, it was suggested that there were three hypothetical negative unpublished cohorts that distorted the symmetry of the funnel plot. When these cohorts were incorporated to produce a hypothetically symmetrical funnel plot, the association between SUA and type 2 diabetes was modestly attenuated (RR 1.10 [95% CI 1.03–1.20]) but remained statistically significant ($P = 0.009$).

CONCLUSIONS — Our meta-analysis is the first to summarize the quantitative relationship between SUA level and risk of type 2 diabetes, indicating that each 1 mg/dl increase in SUA resulted in a 17% increase in the risk of type 2 diabetes. Table 3 compares other risk factors of type 2 diabetes, established from meta-analysis or systematic review (26–29), with SUA. Interestingly, the effect of a 1 mg/dl increment in SUA has been found to be comparable to a 1 kg/m^2 increment in BMI.

Pathologically and epidemiologically, it has been indicated that elevated SUA concentration is correlated with lifestyle factors (high alcohol intake [30] in particular) and various metabolic profiles (especially high values of BMI, blood pressure, fasting plasma glucose and triglycerides, and low HDL cholesterol values [31,32], which are typically considered to be diagnostic criteria for metabolic syndrome [33]). Therefore, it is possible to establish whether the observed positive association between SUA level and risk of type 2 diabetes is noncausal. Our sensitivity analysis indicated that a significant association was observed if analyses were limited to studies that included adjustment for alcohol intake or sufficient metabolic confounders (i.e., more than three metabolic confounders among BMI, fasting plasma glucose, hypertension [or systolic blood pressure], HDL cholesterol, and triglycerides), although the adjustment weakened the association. Therefore, the results of this analysis strongly suggest that SUA is an independent predictor of the development of type 2 diabetes. Therefore, these findings suggest that there are both noncausal and causal associations between SUA level and the risk of type 2 diabetes.

The limitations of this meta-analysis must be considered. First, the overall effect estimated by the current analysis might be inaccurate due to the statistically significant publication bias. According to the results of the compensatory trim-and-fill method, the overall RR of type 2 diabetes for each 1 mg/dl SUA increase should be scaled downward by 0.07 to

Table 3—*Comparison of other risk factors of type 2 diabetes with incremental increase in SUA*

Risk factor	RR	To how much of mg/dl in SUA is the RR comparable?
Obesity (ref. 26)		
BMI (per kg/m^2)	1.16	1.0
Waist circumference (per cm)	1.06	0.4
High alcohol intake (ref. 29)		
>3 drinks/day vs. 1 to 3 drinks/day	1.43	2.3
Physical inactivity (ref. 27)		
The lowest vs. the highest level of moderate-intensity physical activity*	1.20†	1.2
Smoking (ref. 28)		
Heavy smokers (≥20 cigarettes/day) versus nonsmokers	1.61	3.1
Light smokers (<20 cigarettes/day) versus nonsmokers	1.29	1.7
Former smoker versus nonsmokers	1.23	1.4

*Typically, no walking versus ≥2.5 h/week brisk walking. †This RR is adjusted for BMI.

adjust for publication bias. However, this method may overestimate the magnitude of any publication bias (34). Moreover, this method did not change the statistical significance of the association between SUA level and development of type 2 diabetes. Therefore, the effect of adjustment for publication bias was probably modest. Second, the odds and risk ratios were combined as indicators of RR. The odds ratio overestimates the risk ratio, especially when the outcome of interest is common. It is possible that this method could distort the overall and stratified analyses within cohort design. The overestimation is, however, of little practical importance and can be ignored as long as the pooled risk ratio is near to 1 and the total incidence is relatively rare (<10%), as they were in our meta-analysis (5). Third, in the sensitivity analysis, the statistical power might be insufficient to explain the source of the large study heterogeneity because of the small number of data units within strata. For example, there was a substantially larger increase in the risk of elevated SUA for development of type 2 diabetes observed in Western countries (RR 1.27) compared with Asian countries (RR 1.09) and for women (RR 1.28) compared with men (RR 1.09). Although these differences were statistically insignificant, we cannot exclude the possibility of the influence of race or sex on the association between SUA level and type 2 diabetes. This issue might be solved by a patient-level meta-analysis, which would be beyond the current meta-analysis. Fourth, there were few studies that included a consideration of significant confounders influencing SUA level, such as serum creatinine and drugs (e.g., diuretic agents or alloprinol). These confounders could contribute to modification of the association between SUA and risk of type 2 diabetes. Fifth, we thought it was too early to determine whether there is a cutoff level in SUA to increase or reduce the risk of development of type 2 diabetes because of both the limited number of studies that used SUA level as a categorical variable and provided RR data for each category and the variation in methods of how SUA levels in each subject were categorized. Therefore, we cannot rule out the possibility that SUA level has a threshold effect on the risk of type 2 diabetes rather than a dose-response effect.

In conclusion, our meta-analysis suggests that SUA level is independently associated with the development of type 2 diabetes. It is possible that these findings are the first step to utilizing SUA, which has been suggested to be a risk factor for type 2 diabetes, in primary care medical practice. Further research should attempt to investigate whether SUA would be useful for predicting type 2 diabetes with respect to the prevention of type 2 diabetes; for example, studies should aim to specify the population for which the SUA level is especially important and to determine the SUA threshold for increased risk of type 2 diabetes.

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Low HDL Cholesterol Is Associated With the Risk of Stroke in Elderly Diabetic Individuals

Changes in the risk for atherosclerotic diseases at various ages

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OBJECTIVE — To clarify the relationship between lipid levels and ischemic heart disease (IHD) and cerebrovascular disease (CVD) in diabetic individuals.

RESEARCH DESIGN AND METHODS — The Japan Cholesterol and Diabetes Mellitus Study is a prospective cohort study of 4,014 type 2 diabetic patients (1,936 women; mean ± SD age 67.4 ± 9.5 years). Lipid and glucose levels and other factors were investigated in relation to occurrence of IHD or CVD.

RESULTS — IHD and CVD occurred in 1.59 and 1.43% of participants, respectively, over a 2-year period. The relation of lower HDL or higher LDL cholesterol to occurrence of IHD in subjects <65 years old was significant. Lower HDL cholesterol was also significantly related to CVD in subjects ≥65 years old and especially in those >75 years old (n = 1,016; odds ratio 0.511 [95% CI 0.239–0.918]; $P < 0.05$). Stepwise multiple regression analysis with onset of CVD as a dependent variable showed the same result.

CONCLUSIONS — Lower HDL cholesterol is an important risk factor for not only IHD but also CVD, especially in diabetic elderly individuals.

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Type 2 diabetes, dyslipidemia, and aging are independent risk factors for cardiovascular diseases. Japanese individuals have lower rates of ischemic heart disease (IHD) and higher rates of cerebrovascular disease (CVD); however, diabetic individuals have an increased risk of IHD (1,2). Risk factors for IHD or CVD in elderly diabetic individuals are not fully known (3), and the Japan Cholesterol and Diabetes Mellitus Study was formulated to evaluate them (Umin Clinical Trials Registry, clinical trial reg. no. UMIN00000516; http://www.umin.ac.jp/ctr/index.htm).

RESEARCH DESIGN AND METHODS

— The Japan Cholesterol and Diabetes Mellitus Study is a single-center prospective cohort study comprised of 4,014 Japanese diabetic individuals on a consecutive outpatient basis recruited between September 2004 and March 2005 (1,936 women; mean ± SD age 67.4 ± 9.5 years [range 35–83 years]). Patients with previous IHD (myocardial infarction, unstable angina pectoris, angioplasty, or bypass grafting) or CVD (stroke) were excluded. Follow-up information was available for 98.2 and 92.3% of patients enrolled in the first and second years, respectively. Patients were divided into those aged <65 years, 65–74 years, and >75 years (n = 1,267, 1,731, and 1,016, respectively). The primary end points were onset of IHD or CVD. Plasma lipid, glucose, A1C, and other relevant levels were measured annually.

The study was approved by institutional review boards and by the safety-monitoring board. All events were confirmed by the organizing committee annually. The guidelines of the Japan Atherosclerosis Society (2002), stating that LDL cholesterol should be <120 mg/dl and HDL cholesterol >40 mg/dl in diabetic individuals, and the American Diabetes Association criteria for diagnosis of type 2 diabetes were used (4,5).

Results are presented as means ± SD. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC). Incidences were analyzed in relation to risk factors. Univariate and multiple logistic regression analysis and stepwise analysis were used. Values of $P < 0.05$ were considered significant.

RESULTS

— Mean A1C, fasting plasma glucose, LDL cholesterol, triglyceride, HDL cholesterol, and systolic and diastolic blood pressure levels on registration were 7.53 ± 1.12%, 159.4 ± 52.7

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Table 1—*Adjusted multiple regression analyses of factors found to be significant by univariate regression analysis for IHD or CVD, as well as major atherogenic risk factors; total* n = *4,014*

	<65 years old (n = 1,276)		65–74 years old (n = 1,731)		≤75 years old (n = 1,016)	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
IHD						
Sex	1.469 (1.02–1.94)	0.02*	1.109 (1.02–1.74)	0.04*	0.829 (0.23–3.06)	0.78
Age	1.063 (0.96–1.20)	0.28	0.991 (0.86–1.15)	0.99	0.996 (0.83–1.17)	0.87
LDL cholesterol	1.225 (1.02–2.04)	0.04*	1.001 (0.72–1.25)	0.89	0.776 (0.43–1.40)	0.40
HDL cholesterol	0.659 (0.39–0.98)	0.04*	0.939 (0.68–1.25)	0.38	0.946 (0.58–1.29)	0.23
Triglycerides	1.356 (1.00–2.02)	0.05	0.731 (0.52–1.94)	0.18	0.881 (0.46–1.70)	0.71
A1C	1.179 (0.75–1.88)	0.27	1.082 (0.76–1.55)	0.67	1.274 (0.57–2.35)	0.44
SBP	0.702 (0.49–1.09)	0.15	1.082 (0.79–1.69)	0.15	1.051 (0.58–1.89)	0.87
DBP	1.020 (0.97–1.05)	0.28	1.088 (0.73–1.27)	0.24	1.998 (0.99–4.35)	0.08
CVD						
Sex	1.158 (0.68–2.17)	0.47	1.004 (0.79–1.69)	0.82	0.847 (0.45–1.52)	0.58
Age	1.006 (0.94–1.10)	0.88	0.982 (0.82–1.14)	0.39	1.139 (0.99–1.30)	0.06
LDL cholesterol	1.099 (0.98–1.23)	0.06	1.067 (0.76–1.44)	0.51	1.128 (0.64–1.59)	0.71
HDL cholesterol	0.888 (0.64–1.48)	0.09	0.758 (0.53–0.98)	0.04*	0.511 (0.24–0.92)	0.04*
Triglycerides	1.147 (0.68–2.04)	0.62	1.070 (0.69–1.67)	0.75	1.355 (0.75–2.56)	0.32
A1C	0.996 (0.64–1.28)	0.52	1.019 (0.75–1.74)	0.54	1.015 (0.60–1.72)	0.95
SBP	1.005 (0.67–1.33)	0.86	0.991 (0.94–1.13)	0.35	1.063 (0.62–1.57)	0.75
DBP	1.109 (0.61–2.13)	0.74	1.303 (0.81–2.09)	0.27	1.045 (0.68–1.5)	0.59

	IHD				CVD			
	<65 years old	65–74 years old	≤75 years old	Total	<65 years old	65–74 years old	≤75 years old	Total
HDL cholesterol (mg/dl)								
<44	2.31	2.49	1.68	2.14	1.13	1.99	2.62*	2.01
44–53	1.45	1.45	1.64	1.50	1.05	1.84	2.15*	1.64
54–63	1.25	1.41	0.98	1.23	1.44	0.80	0.88*	1.04
≥64	0.42	1.69	0.99	1.19	1.0	0.80	0.45*	0.72

Data were adjusted for sex. The ratio of male to female subjects is 1:1. *Statistically significant (P <0.05). DBP, diastolic blood pressure; SBP, systolic blood pressure.

mg/dl, 120.3 ± 32 mg/dl, 140.6 ± 108.3 mg/dl, 55.8 ± 18.0 mg/dl, 136.5 ± 17.1 mmHg, and 75.1 ± 11.1 mmHg, respectively. Insulin and oral agents for diabetes were prescribed for 19.9 and 70.5% of individuals, respectively. Dyslipidemia was seen in 79.1%, and antihyperlipidemic drugs were prescribed in 59.0%. Mean lipid and glucose metabolism levels did not change significantly over the 2-year study period.

In the first and second years, 83 and 69 vascular events occurred, respectively. IHD and CVD occurred in 0.80 and 0.71% of total patients per year. The relationship between IHD or CVD and background factors such as LDL cholesterol levels in each age-group was analyzed by univariate logistic regression.

Sex, age, LDL cholesterol, HDL cholesterol, and triglyceride were significantly related to IDH in patients aged <65 years. Age, sex, history of hypertension, and antihypertensive drugs were related in patients aged between 65 and 74 years, and sex and systolic and diastolic blood pressure were related in patients aged > 75 years. CVD and LDL cholesterol were related in patients aged <65 years, and HDL cholesterol and systolic blood pressure were related in patients aged >75 years.

We performed multiple regression analysis with factors found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors (A1C, etc.) in three age-groups (Table 1). LDL and HDL cholesterol were associated with IHD in patients aged < 65 years but not in other age-groups. Sex was associated with IHD in individuals aged <74 years. HDL cholesterol was also associated with CVD in individuals between aged between 65 and 74 years and >75 years.

Stepwise multiple regression analysis was performed using factors that were found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors. HDL and LDL cholesterol were associated with IHD in individuals aged <65 years (HDL cholesterol odds ratio 0.79 [95% CI 0.58–0.96; P = 0.04] and LDL cholesterol 0.60 [0.33–0.99; P = 0.04]). HDL cholesterol was associated with CVD in individuals aged between 65 and 74 years and ≥75 years (65–74 years 0.73 [0.56–0.94; P = 0.04] and ≥75 years 0.60 [0.35–0.91; P = 0.01]).

The relation of age or HDL cholesterol to IHD and CVD was evaluated in quartile categories. HDL cholesterol levels were inversely correlated with IHD in individuals aged <65 years (hazards ratio 0.633 [95% CI 0.428–0.975]) but not in other groups. The relationship between CVD and HDL cholesterol was prominent in those aged >75years but not in other age-groups (Table 1). There were no sex-related differences in the relationship of HDL cholesterol with CVD. There was no relationship between LDL, triglyceride, fasting blood glucose, or A1C and the frequency of CVD.

CONCLUSIONS — This study represents one of the largest-scale attempts to examine IHD and CVD in middle-aged and elderly diabetic individuals. In the U.S., evidence suggests that middle-aged diabetic individuals have an IHD risk similar to that for individuals with myocardial infarction (6). However, this risk may not exist in elderly diabetic individuals. Many guidelines to prevent atherothrombotic diseases recommend strict control of LDL cholesterol in diabetic patients but the same guideline for HDL cholesterol control (40 mg/dl) as that used for nondiabetic subjects (4–7).

A novel finding was that type 2 diabetic elderly individuals had frequent CVD, and incidence rates were associated with HDL cholesterol. Few data were available for the relationship among elderly, type 2 diabetes, and CVD (8,9).

There have been three large-scale clinical studies of statins that included participants aged up to 75 years (10–12). Although they reported that statins exerted effects on IHD (including in diabetic individuals), effects were not pronounced. (Prosper reported that statins induced a 16% decrease in IHD without any effects on CVD.) The data suggest that because LDL cholesterol decreased, simple LDL cholesterol control may not prevent IHD or CVD in elderly individuals. Our study shows the importance of HDL cholesterol in CVD in elderly diabetic individuals and in IHD in middle-aged diabetic individuals. If HDL cholesterol is well controlled in elderly diabetic patients, then CVD and IHD might be decreased to the levels found in middle-aged cohorts. Patients prescribed statins whose HDL cholesterol was <40 mg/dl showed the same risk (data not shown). Although medicated patients may be more conscious of diseases, HDL cholesterol is a strong risk factor and masks the effects of statins.

In conclusion, HDL and LDL cholesterol were risk factors for IHD in diabetic patients aged <65 years. In addition, HDL cholesterol was a risk factor for CVD in elderly diabetic subjects, especially those aged >75 years. HDL cholesterol may help prevent CVD in elderly diabetic subjects. Risk factors for IHD and CVD appear to change with advancing age.

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No potential conflicts of interest relevant to this article were reported.

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Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women: A Meta-analysis

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Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women

A Meta-analysis

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Context Epidemiological studies have indicated an inverse association between cardiorespiratory fitness (CRF) and coronary heart disease (CHD) or all-cause mortality in healthy participants.

Objective To define quantitative relationships between CRF and CHD events, cardiovascular disease (CVD) events, or all-cause mortality in healthy men and women.

Data Sources and Study Selection A systematic literature search was conducted for observational cohort studies using MEDLINE (1966 to December 31, 2008) and EMBASE (1980 to December 31, 2008). The Medical Subject Headings search terms used included *exercise tolerance, exercise test, exercise/physiology, physical fitness, oxygen consumption, cardiovascular diseases, myocardial ischemia, mortality, mortalities, death, fatality, fatal, incidence,* or *morbidity*. Studies reporting associations of baseline CRF with CHD events, CVD events, or all-cause mortality in healthy participants were included.

Data Extraction Two authors independently extracted relevant data. CRF was estimated as maximal aerobic capacity (MAC) expressed in metabolic equivalent (MET) units. Participants were categorized as low CRF (<7.9 METs), intermediate CRF (7.9-10.8 METs), or high CRF (≥10.9 METs). CHD and CVD were combined into 1 outcome (CHD/CVD). Risk ratios (RRs) for a 1-MET higher level of MAC and for participants with lower vs higher CRF were calculated with a random-effects model.

Data Synthesis Data were obtained from 33 eligible studies (all-cause mortality, 102 980 participants and 6910 cases; CHD/CVD, 84 323 participants and 4485 cases). Pooled RRs of all-cause mortality and CHD/CVD events per 1-MET higher level of MAC (corresponding to 1-km/h higher running/jogging speed) were 0.87 (95% confidence interval [CI], 0.84-0.90) and 0.85 (95% CI, 0.82-0.88), respectively. Compared with participants with high CRF, those with low CRF had an RR for all-cause mortality of 1.70 (95% CI, 1.51-1.92; $P<.001$) and for CHD/CVD events of 1.56 (95% CI, 1.39-1.75; $P<.001$), adjusting for heterogeneity of study design. Compared with participants with intermediate CRF, those with low CRF had an RR for all-cause mortality of 1.40 (95% CI, 1.32-1.48; $P<.001$) and for CHD/CVD events of 1.47 (95% CI, 1.35-1.61; $P<.001$), adjusting for heterogeneity of study design.

Conclusions Better CRF was associated with lower risk of all-cause mortality and CHD/CVD. Participants with a MAC of 7.9 METs or more had substantially lower rates of all-cause mortality and CHD/CVD events compared with those with a MAC of less 7.9 METs.

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CORONARY HEART DISEASE (CHD) is a major cause of disability and premature death throughout the world.[1] Epidemiological studies have demonstrated an inverse association between physical fitness and the incidence of CHD or all-cause mortality in healthy or asymptomatic participants. Physical fitness is typically expressed as cardiorespiratory fitness (CRF) and is assessed by exercise tolerance testing[2]; however, it is rare for clinicians to consider CRF when evaluating future risk of CHD.[3]

A major reason for lack of consideration of CRF as a marker of CHD risk may be that the quantitative association of CRF for cardiovascular risk is not well established. The degree of risk reduc-

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tion associated with each incremental higher level of CRF, the criteria for low CRF, and the magnitude of risk associated with low CRF have been inconsistent among studies. Our goal of this meta-analysis was to systematically review the quantitative relationship between CRF and all-cause mortality and CHD or cardiovascular disease (CVD) events in healthy individuals.

METHODS

Search Strategy

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology.[4] We performed a systematic literature search of MEDLINE (1966 to December 31, 2008) and EMBASE (1980 to December 31, 2008) for observational cohort studies. Three search themes were combined using the Boolean operator *and*. The first keywords were related to CRF (combined exploded versions of the Medical Subject Headings [MeSH] as follows: *exercise tolerance* OR *exercise test* OR *exercise/physiology* OR *physical fitness* OR *oxygen consumption*); the second keywords were related to the outcome of this meta-analysis (combined unexploded version of MeSH [*cardiovascular diseases*] or the exploded version of MeSH [*myocardial ischemia*]) or the following text words (*mortality* OR *mortalities* OR *death* OR *fatality* OR *fatal* OR *incidence** OR *event** OR *morbidity*); and the third keywords were related to risk estimates (combined text words as follows: *regression analysis* OR *regression model** OR *statistical regression** OR *logistic regression** OR *logit regression** OR *logistic model** OR *logit model** OR *Cox model* OR *hazard model* OR *odds ratio** OR *ORs* OR *relative odds* OR *risk ratio** OR *relative risk** OR *RRs*). We also included studies published in non-English language. In addition, we searched the reference lists of all identified relevant publications.

Inclusion and Exclusion Criteria

We included papers if (1) CRF was assessed by an exercise stress test; (2) the association of CRF with all-cause mortality and with CHD or CVD was evaluated; (3) CRF could be assessed as maximal aerobic capacity (MAC), expressed in units of metabolic equivalents (METs), which is defined as the ratio of intensity of physical activity to that of sitting at rest; and (4) risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) relating to each category of MAC were reported or could be calculated. We excluded studies that were intended only for patients having a specific disease that presented a major risk factor, such as diabetes, hypertension, and familial hypercholesteremia, as well as studies that included patients with CHD or chronic heart failure.

To avoid double counting of a cohort, study selection was limited to a single set of results when multiple publications were available for a single observational study. The first priority for selection was the study with the longest follow-up and the second was the study with full cohort analysis covering the largest number of participants among articles from a single cohort. We conducted 2 separate meta-analyses for risk of all-cause mortality and CHD or CVD in relation to CRF. When an individual study provided data on both CHD or myocardial infarction (MI) and CVD,[5-7] priority for data abstraction was given to CVD because CVD is more comprehensive than CHD and MI. Similarly, if data on both events and deaths were provided,[6,8,9] priority was given to events.

We combined CHD and CVD into 1 outcome (CHD/CVD), which included studies whose outcome was a CVD event, CVD death, CHD event, or CHD death, because the number of eligible studies included was limited. Although criteria for the end point in CHD varied from study to study, the end points that we specified as CHD outcome in our meta-analysis were (1) death from MI; (2) death from CHD including MI; and (3) a CHD event, a term which meant either death from CHD, sudden cardiac death, occurrence of nonfatal CHD, or nonfatal MI. Additionally, we included studies whose outcome was either CVD death (ie, encompassing death from cardiovascular causes other than CHD) or CVD events (ie, lumping together fatal and nonfatal CVD).

Data Abstraction

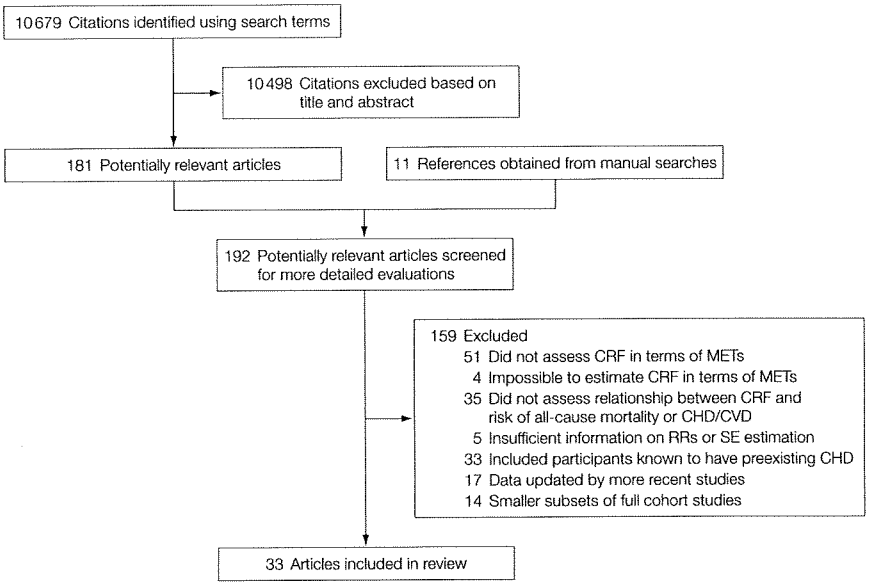
Data abstracted were the first author's name, year of publication, country of origin, specific outcomes, duration of follow-up, methods for outcome assessment, instrument or methods for measurement of CRF, whether maximal exercise testing (defined as instructing participants to continue exercise until their maximal workload) was conducted, mean of participants' age, proportion of men, number of participants and number of new cases (ie, deaths or events) during the observational periods, adjusted variables, and whether participants with abnormal electrocardiogram findings (ie, ST elevation/depression) during exercise testing were included. Two of our investigators (S. Kodama and H. Sone) independently reviewed each published paper and extracted relevant information. Any disagreement was resolved by consensus.

In studies using CRF as a categorical variable, we standardized all reported RRs into comparison of the risk of the lower CRF group with that in the higher CRF group. Therefore, when the lowest CRF group was referent, we converted the reported RR into its reciprocal. When a study provided several RRs, such as unadjusted and adjusted RRs, the most completely adjusted RR was used. The standard error (SE) of each RR was derived from 95% CIs or *P* values. If data related to RR and its corresponding SE were not provided, their value was directly calculated using data on the number of participants (P) and new cases (C) of risk and the reference (ref) groups in each comparison, using the equation:

$$RR = [(C_{risk}/P_{risk})/(C_{ref}/P_{ref})],\ SE^2 = [(1/C_{risk})-(1/P_{risk})]+[(1/C_{ref})-(1/P_{ref})].$$

The MAC was calculated from the exercise workload at the termination of exercise testing and relative exercise intensity (ie, proportion of the workload to MAC). The exercise workload was converted into MET units (1 MET corresponds to 3.5 mL/min/kg of oxygen consumption [$\dot{V}O_2$]), according to the Metabolic Calculation Handbook by

Figure 1. Selection of Articles for Meta-analysis



CHD indicates coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; METs, metabolic equivalents; and RRs, risk ratios.

the American College of Sports Medicine.[10] Relative exercise intensity was estimated using a linear equation according to Swain et al[11]:

heart rate at exercise/maximal heart rate = 0.64 × ($\dot{V}O_2$ at exercise/maximal $\dot{V}O_2$).

For some specific exercise stress tests, the MAC was directly estimated using the prediction equation determined by a previous validation study for each protocol of the exercise test (the Balke treadmill test,[12,13] the modified Bruce test,[14] and the Canadian Home Fitness test[15]).

When exposure was expressed as a range, we converted it into point estimates expressed as average exposure using the midpoint of the range except for the lowest and highest fit group. If data on the average value were not available, it was estimated by the assumption that the MAC levels of the study population had a normal distribution using the mean value and its SD of each study sample. This assumption is consistent with a prior study.[16] However, if the SD was not available, we assumed that its value equaled 2 METs, according to the statement of the American Heart Association.[17]

After converting all exposures into MET units, we additionally adjusted MET units for age and sex. According to a Statement for Healthcare Professionals From the American Heart Association,[17] we assumed that the MAC is 2 METs lower in women than in men and that for each year of aging, it decreased by 0.1 MET based on a prior study.[18] Finally, we represented CRF as the adjusted MAC under the assumption that all participants were 50-year-old men in the analyses described below.

Dose-Response and Categorical Analyses

We first performed dose-response analyses by summarizing how much risk reduction could be predicted per incremental increase in CRF. The study-specific RR for each higher MET (corresponding to 1-km/h higher running/jogging speed) in MAC, if not reported, was estimated by regressing the natural logarithm of the RR (lnRR) according to each CRF category against its corresponding mean MAC value, using the method described by Greenland and Longnecker.[19]

We then performed categorical analyses to summarize the risk of all-cause mortality and CHD/CVD for low CRF. We assigned every RR reported in each study to 1 of the following 3 comparisons based on the CRF level of risk and reference group: (1) low vs high CRF, (2) low vs intermediate CRF, and (3) intermediate vs high CRF. This method is based on a previous meta-analysis of the relationship between activity level and stroke risk.[20] For studies that presented risk estimates for more than 2 CRF categories, the ranges of the adjusted MAC of the lowest, highest, and in-between categories defined by each study were 5.5 to 7.8, 11.0 to 15.2, and 7.9 to 10.7 METs, respectively; except that in 2 studies,[21,22] the second highest category of CRF was more than 11.0 METs and, in 1 study,[7] the highest category of CRF was 10.6 METs.

To avoid overlap of the CRF range of the 3 categories, we defined low, intermediate, and high CRF as less than 7.9 METs, 7.9 to 10.8 METs, and 10.9 METs or more, respectively. Consequently, we could assign every RR in each study to 1 of the 3 predefined subgroups with 2 exceptions. In 2 studies,[21,22] the mean MAC values for both the highest and the second highest category were the same as the high CRF category (defined by ≥10.9 METs). Therefore, RR data for comparison between 2 CRF categories could not be included in our categorical analysis for these 2 studies.

Statistical Analysis

The pooled RRs for a 1-MET higher level of MAC and the lower CRF in comparison with the higher CRF within each of the 3 comparisons were estimated by using a fixed-effects or random-effects model.[23] If significant heterogeneity of RRs that was tested by calculating the I^2 statistic[24] was present, we chose the pooled estimates from the random-effects model because it is better than the fixed-effects model and it explains between-study heterogeneity.

To examine the effect of study characteristics on risk reduction per 1-MET higher level of MAC, sensitivity analyses were conducted for the possible confounders (mean age [≥50 years or not], sex [only men or not], adjustment for smoking [yes or no], adjustment for multiple confounders, defined as adjustment

Table 1. Characteristics of Studies Included in the Meta-analysis

Source (Location)	No. of Participants	Men, %	Mean (or Midpoint) Age, y	Mean Follow-up, y	Methods for Outcome Measures	Specific Outcomes (CHD/CVD Criteria)	No. of Events for Each Outcome	Instrument for Assessing CRF	Whether Max or Sub Reached[a]
Aijaz et al,[29] 2008 (US)	8620	73	52	16	Registry	All-cause mortality	535	Treadmill	Max
Aktas et al,[30] 2004 (US)	3554	81	57	8	Registry	All-cause mortality	114	Treadmill	Sub
Allen et al,[31] 1980 (US)									
Men	350	100	NA	1.1	Questionnaire	CHD event (MI, sudden cardiac death)	34	Ergometer	Max
Women	302	0	NA				10		
Arraiz et al,[32] 2004 (Canada)	NA	NA	47	7	Registry	All-cause mortality; CVD death (NA)	55; 37	Canadian Home Fitness Test	Sub
Balady et al,[33] 2004 (US)									
Men	1431	100	45	18.2	Hospital record	CHD event (onset of AP, coronary insufficiency, MI)	224	Treadmill	Sub
Women	1612	0	45				81		
Bruce et al,[34] 1980 (US)	2365	100	45	5.6	Questionnaire	CHD event (NA)	47	Treadmill	Max
Cumming et al,[35] 1975 (Canada)	486[b]	100	53	3	Questionnaire	CHD event (NA)	26	Ergometer	Max
Erikssen et al,[36] 1998 (Norway)	1428	100	57	13	Registry	All-cause mortality; CVD death (CHD, stroke, the other CVD)	238; 120	Ergometer	Max
Erikssen et al,[37] 2004 (Norway)	2014	100	49	26	Questionnaire and registry	CHD death (CHD, sudden cardiac death)	300	Ergometer	Max
Farrell et al,[38] 2004 (US)	6925	0	43	11.4	Registry	All-cause mortality	195	Treadmill	Sub
Gulati et al,[16] 2003 (US)	5721	0	52	8.4	Registry	All-cause mortality	180	Treadmill	Max
Gulati et al,[39] 2005 (US)	5636	0	52	9	Registry	All-cause mortality; CVD death (*ICD-9, ICD-10*)	171; 52	Treadmill	Max
Gulati et al,[40] 2005 (US)	5721	0	52	8.4	Registry	CVD death (NA)	180	Treadmill	Max
Gyntelberg et al,[41] 1980 (Denmark)	5249	100	50	5	Registry	CHD event (MI, sudden cardiac death)	170	Ergometer	Sub
Hein et al,[42] 1992 (Denmark)	4999	100	48	17	Registry	All-cause mortality	941	Ergometer	Sub
Jouven et al,[43] 2005 (France)	5713[b]	100	48	23	Hospital record	CHD death (MI death)	210	Ergometer	Sub
Kampert et al,[44] 1996 (US)	25 341	100	43	8.4	Registry	All-cause mortality	601	Treadmill	Sub
Katzmarzyk et al,[45] 2005 (US)	19 173	100	43	10.2	Registry	All-cause mortality	477	Treadmill	Sub
Laukkanen et al,[8] 2007 (Finland)	1639	100	52	16.6	Registry	All-cause mortality; CVD event (*ICD-9, ICD-10*)	304; 340	Ergometer	Max
Laukkanen et al,[9] 2008 (Finland)	1639	100	52	16.6	Registry	All-cause mortality; CVD event (*ICD-9, ICD-10*)	304; 340	Ergometer	Max
Miller et al,[6] 2005 (UK)	578	100	52	7.3	Questionnaire, registry, and hospital record	All-cause mortality; CVD event (*ICD-9*)	68; 62	Ergometer	Sub
Mora et al,[46] 2003 (US)	2994	0	55	20.3	Questionnaire and registry	All-cause mortality; CVD death (NA)	427; 147	Treadmill	Sub
Myers et al,[47] 2002 (US)	2534[b]	100	56	6.2	Registry	All-cause mortality	288	Treadmill and ergometer	Sub
Peters et al,[48] 1983 (US)	2779	100	45	4.8	Hospital record	CHD event (MI, sudden cardiac death)	36	Ergometer	Sub
Rywik et al,[49] 2002 (US)	1083	57	52	8.8	Registry	CHD event (AP, MI, sudden cardiac death)	76	Treadmill	Max

(continued)

Table 1. Characteristics of Studies Included in the Meta-analysis (continued)

Source (Location)	No. of Participants	Men, %	Mean (or Midpoint) Age, y	Mean Follow-up, y	Methods for Outcome Measures	Specific Outcomes (CHD/CVD Criteria)	No. of Events for Each Outcome	Instrument for Assessing CRF	Whether Max or Sub Reached[a]
Sandvik et al,[50] 1988 (Norway)	1960[b]	100	50	15.9	Registry	All-cause mortality; CVD death (NA)	271; 143	Ergometer	Max
Sawada and Muto,[51] 1999 (Japan)	9986[b]	100	37	14	Questionnaire	All-cause mortality; CHD death (*ICD-10*)	247; 72	Ergometer	Sub
Slattery and Jacobs,[5] 1988 (US)	2431	100	50	18.5	Registry	All-cause mortality; CHD death (*ICD-8*)	631; 258	Treadmill	Sub
Sobolski et al,[52] 1987 (Belgium)	1476	100	48	5	Registry	CHD event (MI, sudden cardiac death)	19	Ergometer	Sub
Stevens et al,[21] 2002 (US)									
Men	2860	100	45	26	Questionnaire and registry	All-cause mortality; CVD death (*ICD-9*)	682; 270	Treadmill	Sub
Women	2506	0	47				484; 179		
Stevens et al,[22] 2004 (US)	1359	100	49	19	Questionnaire and registry	All-cause mortality; CVD death (*ICD-9*)	211; 98	Treadmill	Sub
Sui et al,[7] 2007 (US)									
Men	20 278	100	44	10.4	Questionnaire	CVD event (MI, stroke, coronary revascularization)	1512	Treadmill	Sub
Women	5909	0	45				159		
Villeneuve et al,[53] 1998 (Canada)	7561	48	45	7	Registry	All-cause mortality	129	Canadian Home Fitness Test	Sub

Abbreviations: AP, angina pectoris; CHD, coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; *ICD-8, International Classification of Diseases, Eighth Revision*; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Statistical Classification of Diseases, 10th Revision*; MI, myocardial infarction; NA, not available.
[a]Max, workload testing was continued until maximal workload; Sub, maximal workload was predicted from findings of submaximal exercise workload.
[b]Including participants with abnormal exercise electrocardiogram (ie, ST elevation/depression).

for >3 factors among obesity, hypertension, total cholesterol or low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and diabetes [yes or no], mean follow-up [≥12 years or <12 years], instrument for assessing CRF [ergometer or others], and maximal exercise testing [yes or no]). To examine the extent to which between-study heterogeneity was explained by these study characteristics, we additionally conducted linear multiple regression analyses by simultaneously entering these confounders as explanatory variables.

Categorical analyses were repeated with multiadjustment for the prespecified confounders to consider the potential heterogeneity of study characteristics among the subgroups (ie, low vs high CRF, low vs intermediate CRF, and intermediate vs high CRF). Tests of interaction were performed to assess whether the association between CRF and the study outcomes varied across these 3 subgroups.

The Begg and Egger tests[25,26] were used for assessment of publication bias (ie, the tendency for positive associations to be published and negative or null associations to be unpublished). We also followed the Duval and Tweedie "trim and fill" procedure[27] as a method of adjustment for suspected publication bias. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they actually existed.

Two-sided $P \leq .05$ was considered statistically significant, except for the test of publication bias for which the recommended levels are $P \leq .10$.[28] Data were analyzed using STATA version 10 (STATA Corp, College Station, Texas).

RESULTS

Literature Search and Study Characteristics

FIGURE 1 shows the number of studies that were identified and excluded at different stages of the selection process. A total of 33 studies[5-9,16,21,22,29-53] were included in our meta-analysis. Characteristics of the 33 selected studies comprising 102 980 participants (range, 486-25 341) and 6910 cases (range, 26-941) for all-cause mortality and 84 323 participants (range, 302-20 278) and 4485 cases (range, 10-1512) for CHD/CVD are shown in TABLE 1. Twenty-one studies* reported all-cause mortality and 24 studies† reported CVD/CHD. Mean age and follow-up duration ranged from 37 to 57 years and 1.1 to 26 years, respectively. Eight studies[8,33,37,39,45,46,49,52] were used for the dose-response analyses only and 4 studies[9,16,40,44] were used for the categorical analyses only. In 20 studies,‡ RRs were adjusted for smoking and in 9 stud-

*References 5, 6, 8, 9, 16, 21, 22, 29, 30, 32, 36, 38, 39, 42, 44-47, 50, 51, 53.
†References 5-9, 21, 22, 31-37, 39-41, 43, 46, 48-52.
‡References 5, 7-9, 16, 21, 22, 30, 32, 33, 37-39, 44-46, 48, 50, 52, 53.

ies,[7-9,16,33,39,46,50,52] there were multiple study confounders (available in an eTable [http://www.jama.com]).

Dose-response Analyses

FIGURE 2 shows the pooled estimates for the reduction in risk of all-cause mortality and CHD/CVD per higher MET of exercise capacity. Pooled RRs of all-cause mortality and CHD/CVD per 1-MET higher level of MAC were 0.87 (95% CI, 0.84-0.90) and 0.85 (95% CI, 0.82-0.88), respectively. There was evidence of statistical heterogeneity of RRs across studies (I^2=82.3%; $P<.001$ for all-cause mortality; I^2=74.7%; $P<.001$ for CHD/CVD).

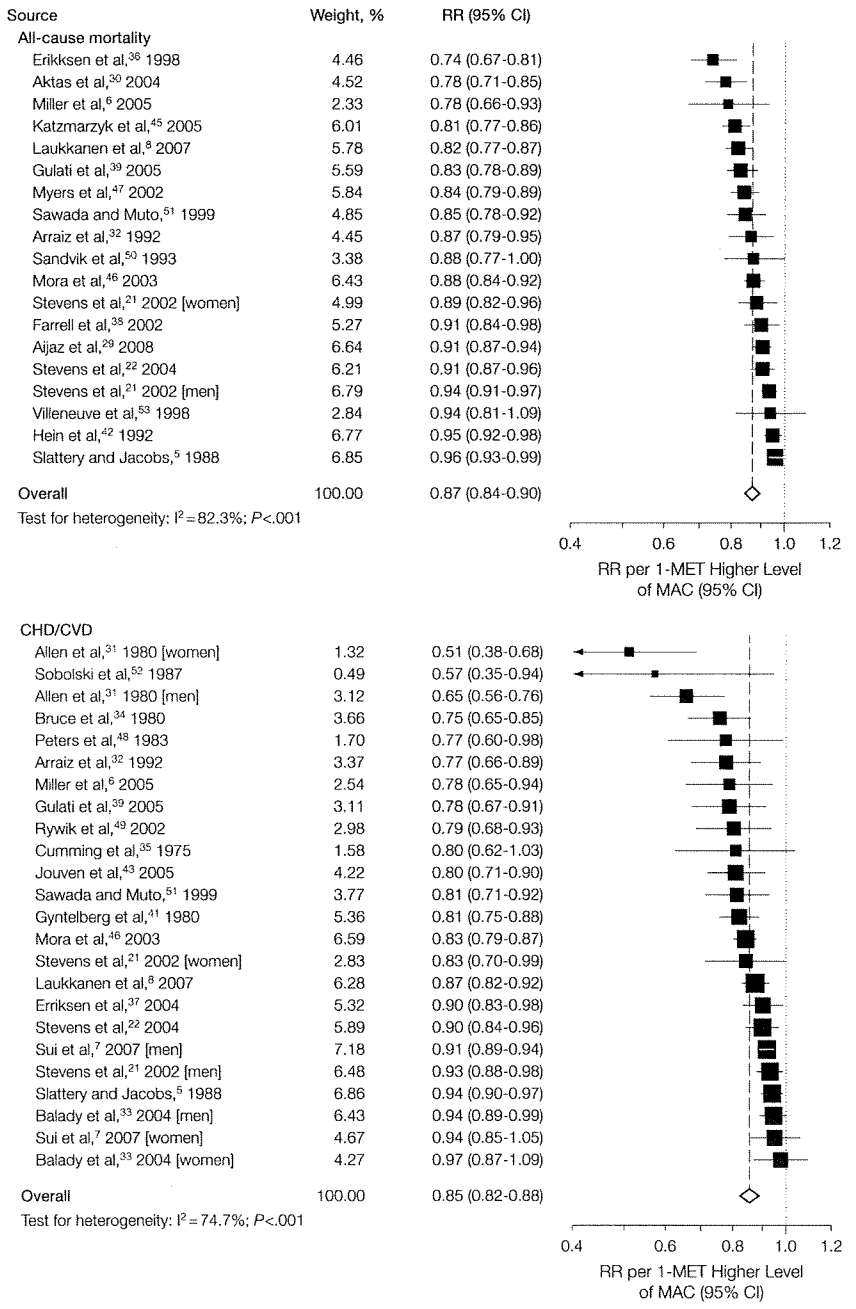
TABLE 2 shows the results of analyses investigating the associations of study characteristics on each outcome. The finding of risk reduction per higher MET for all-cause mortality and CHD/CVD was consistently significant in all of the stratified analyses. However, studies with a follow-up of at least 12 years had weaker associations with study outcomes compared with those that had follow-up of less than 12 years for all-cause mortality ($P=.08$) and CHD/CVD events ($P=.004$). The associations between CRF and risk of CHD/CVD events were stronger in studies that used an ergometer for assessing CRF ($P=.009$) or conducted maximal exercise testing ($P=.02$) and were weaker in studies that were adjusted for smoking ($P=.006$) or multiple metabolic factors ($P=.06$). However, these study characteristics did not influence the associations between MAC and risk of all-cause mortality.

Multiple regression analyses in which all the study characteristics listed in Table 2 were entered as independent variables indicated that study characteristics significantly explained the heterogeneity of the RRs per 1-MET higher level of MAC (all-cause mortality, 79% of total variance; $P=.01$; and CHD/CVD, 67% of total variance; $P=.01$). After adjustment for these study characteristics, there were neither significant differences in risk estimates of CHD/CVD between CHD and CVD (0.89; 95% CI, 0.86-0.92 and 0.89; 95% CI, 0.87-0.90, respectively; $P=.99$) nor between CHD or CVD death and CHD or CVD events (0.88; 95% CI, 0.86-0.90 and 0.90; 95% CI, 0.88-0.91, respectively; $P=.27$).

Categorical Analyses

We performed categorical analyses to summarize the risk of all-cause mortality and CHD/CVD for 3 subgroups (low vs high CRF [FIGURE 3], low vs inter-

Figure 2. Meta-analysis of All-Cause Mortality and CHD/CVD per 1-MET Higher Level of MAC



CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MAC, maximal aerobic capacity; MET, metabolic equivalent; RR, risk ratio. Area of each square is proportional to study weight.

mediate CRF [FIGURE 4], and intermediate vs high CRF [FIGURE 5]). After adjustment for heterogeneity of study characteristics and compared with high and intermediate CRF, respectively, the pooled RRs for the association of low CRF with all-cause mortality were 1.70 (95% CI, 1.51-1.92) and 1.56 (95% CI, 1.39-1.75), respectively. After adjustment for heterogeneity and compared with high and intermediate CRF, respectively, the pooled RRs for the association of low CRF with CHD/CVD events were 1.40 (95% CI, 1.32-1.48) and 1.47 (95% CI, 1.35-1.61), respectively. The pooled RRs for the associations of intermediate CRF with all-cause mortality and CHD/CVD events compared with high CRF were 1.13 (95% CI, 1.04-1.22) and 1.07 (95% CI, 1.01-1.13), respectively. However, tests of the interaction indicated that these estimates for comparisons between intermediate and high risk were significantly lower than for those between low vs high CRF and low vs intermediate CRF ($P<.001$ for any comparisons). Tests of interaction also indicated that there were no significant differences in risk estimates for low vs high CRF compared with low vs intermediate CRF (all-cause mortality, $P=.28$; CHD/CVD, $P=.33$).

Publication Bias

In risk estimates per 1-MET higher level of MAC, there was a statistically significant publication bias according to Egger test (all-cause mortality, $P=.002$; CHD/CVD, $P=.02$). However, adjustment for publication bias by the trim and fill procedure could not detect hypothetical negative unpublished studies that could influence the study. In some of the categorical analyses, statistically significant publication bias was also observed in risk estimates after adjustment for heterogeneity of study characteristics (pooled RR of all-cause mortality for low vs high CRF and low vs intermediate CRF, $P=.03$ by Egger test and $P=.03$ by Begg test, respectively; pooled RR of CHD/CVD for low vs intermediate CRF, $P<.001$ by Egger test). After incorporating the hypothetical studies using trim and fill methods, the risk estimates were attenuated in risk of all-cause mortality for low vs high CRF (RR, 1.48; 95% CI, 1.31-1.68) and low vs intermediate CRF (RR, 1.35; 95% CI, 1.18-1.54), and CHD/CVD for low vs high CRF (RR, 1.38; 95% CI, 1.30-1.45), which suggested the existence of potentially negative studies. Nevertheless, these biases did not change the general conclusions.

COMMENT

Our meta-analysis is the first to our knowledge to quantify CRF as measured by METs, which is a standard scale for expressing exercise workload, and its relationship to all-cause mortality and CHD or CVD events in healthy men and women. According to the dose-response analyses, a 1-MET higher level of MAC was as-

Table 2. Stratified Analyses of Pooled RR of All-Cause Mortality and CVD/CHD for Each MET Higher Level of Maximal Aerobic Capacity

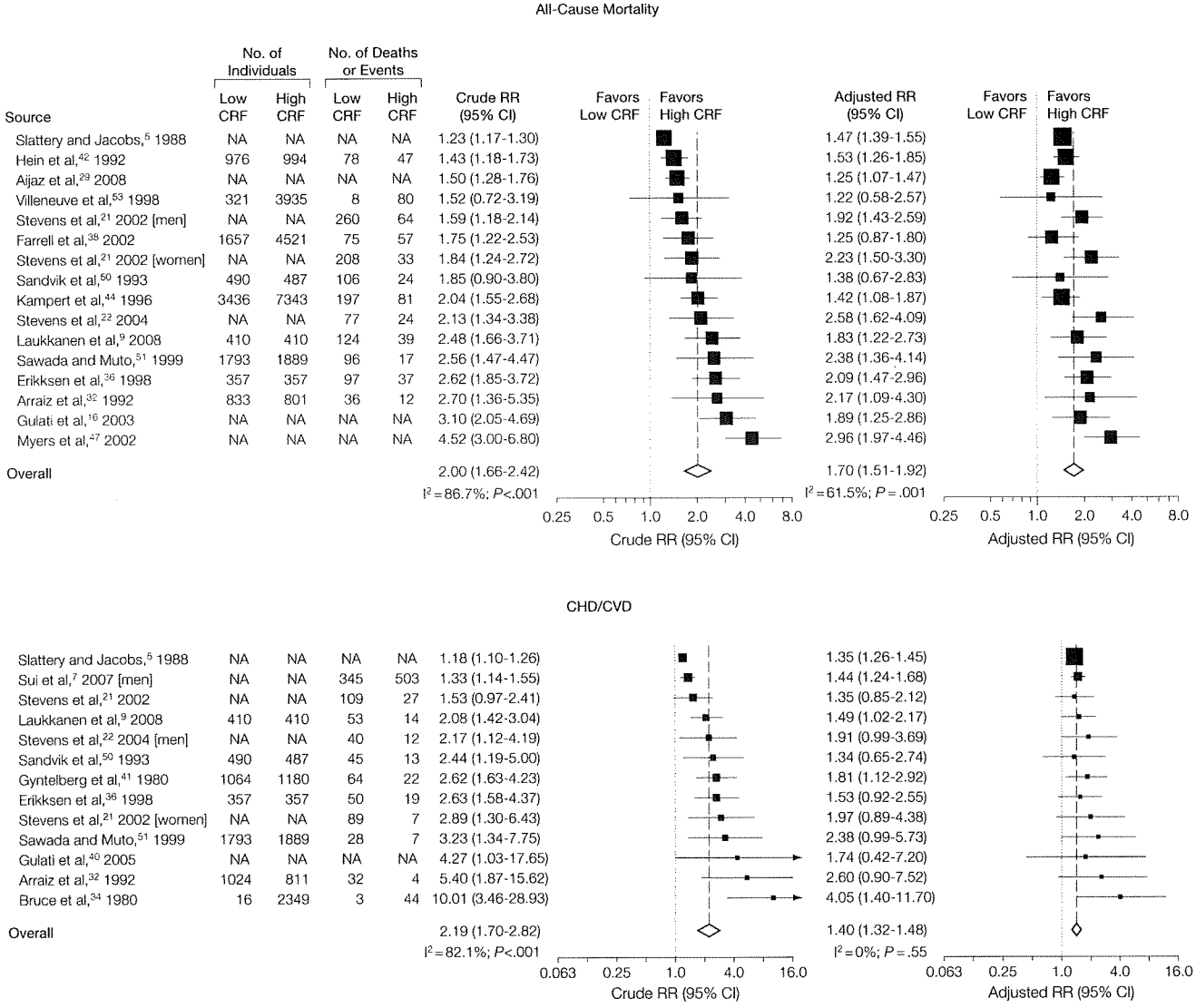
Characteristics	All-Cause Mortality			CHD/CVD		
	No. of Cohorts	RR (95% CI)	*P* Value[a]	No. of Cohorts	RR (95% CI)	*P* Value[a]
Mean age, ≥50 y						
No	10	0.90 (0.86-0.93)	.10	16	0.89 (0.88-0.91)	.80
Yes	9	0.84 (0.80-0.89)		8	0.84 (0.79-0.90)	
Only men						
No	8	0.87 (0.84-0.91)	.88	8	0.84 (0.81-0.87)	.60
Yes	11	0.87 (0.83-0.91)		16	0.86 (0.83-0.89)	
Adjustment for confounders, smoking						
No	7	0.87 (0.83-0.93)	.82	10	0.77 (0.70-0.85)	.006
Yes	12	0.87 (0.84-0.90)		14	0.89 (0.86-0.92)	
>3 Metabolic factors[b]						
No	14	0.86 (0.84-0.89)	.67	16	0.81 (0.77-0.86)	.06
Yes	5	0.86 (0.83-0.89)		8	0.89 (0.85-0.93)	
Patients with abnormal exercise electrocardiogram						
No	10	0.85 (0.81-0.90)	.20	16	0.83 (0.79-0.88)	.40
Yes	9	0.90 (0.86-0.93)		8	0.90 (0.88-0.92)	
Mean follow-up, 12 y						
No	8	0.84 (0.82-0.86)	.08	13	0.78 (0.72-0.84)	.004
Yes	11	0.91 (0.9-0.93)		11	0.89 (0.86-0.92)	
Ergometer used to assess CRF						
No	13	0.90 (0.89-0.92)	.82	13	0.89 (0.86-0.92)	.009
Yes	6	0.88 (0.84-0.91)		11	0.78 (0.73-0.84)	
Whether workload testing was continued until maximal workload						
No	15	0.88 (0.85-0.91)	.24	16	0.88 (0.85-0.91)	.02
Yes	4	0.84 (0.76-0.92)		8	0.77 (0.70-0.85)	

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; RR, risk ratio.
[a] Represents meta-regression for differences across strata.
[b] Means of adjustment for more than 3 coronary risk factors among obesity (or body mass index or waist-to-hip ratio), systolic blood pressure (or hypertension), total cholesterol (or low-density lipoprotein cholesterol or hyperlipidemia), high-density lipoprotein cholesterol, and diabetes.

sociated with 13% and 15% decrements in risk of all-cause mortality and CHD/CVD, respectively. From the clinical viewpoint, these values may be considerable. For example, based on risk estimates of the components of metabolic syndrome according to the National Cholesterol Education Program,[54] these findings suggest that a 1-MET higher level of MAC is comparable to a 7-cm, 5-mm Hg, 1-mmol/L, and 1-mmol/L decrement in waist circumference,[55] systolic blood pressure,[56] triglyceride level (in men),[57] and fasting plasma glucose,[58] respectively, and a 0.2-mmol/L increment in high-density lipoprotein cholesterol.[59] It is possible that prediction of CHD risk could be improved by including CRF with already established risk factors for CHD.

In categorical analyses, individuals with low CRF (<7.9 METs in MAC) had a substantially higher risk of all-cause mortality and CHD/CVD compared with those with intermediate and high CRF (7.9-10.8 and ≥10.9 METs in MAC, respectively). These risk estimates were higher than those for individuals with intermediate CRF compared with those with high CRF, according to the test of interaction. These analyses suggest that a minimal CRF of 7.9 METs may be important for significant prevention of all-cause mortality and CHD/CVD. A previous review suggested that physical activity yielding 1000 kcal energy expenditure per week is needed for signifi-

Figure 3. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Low vs High CRF

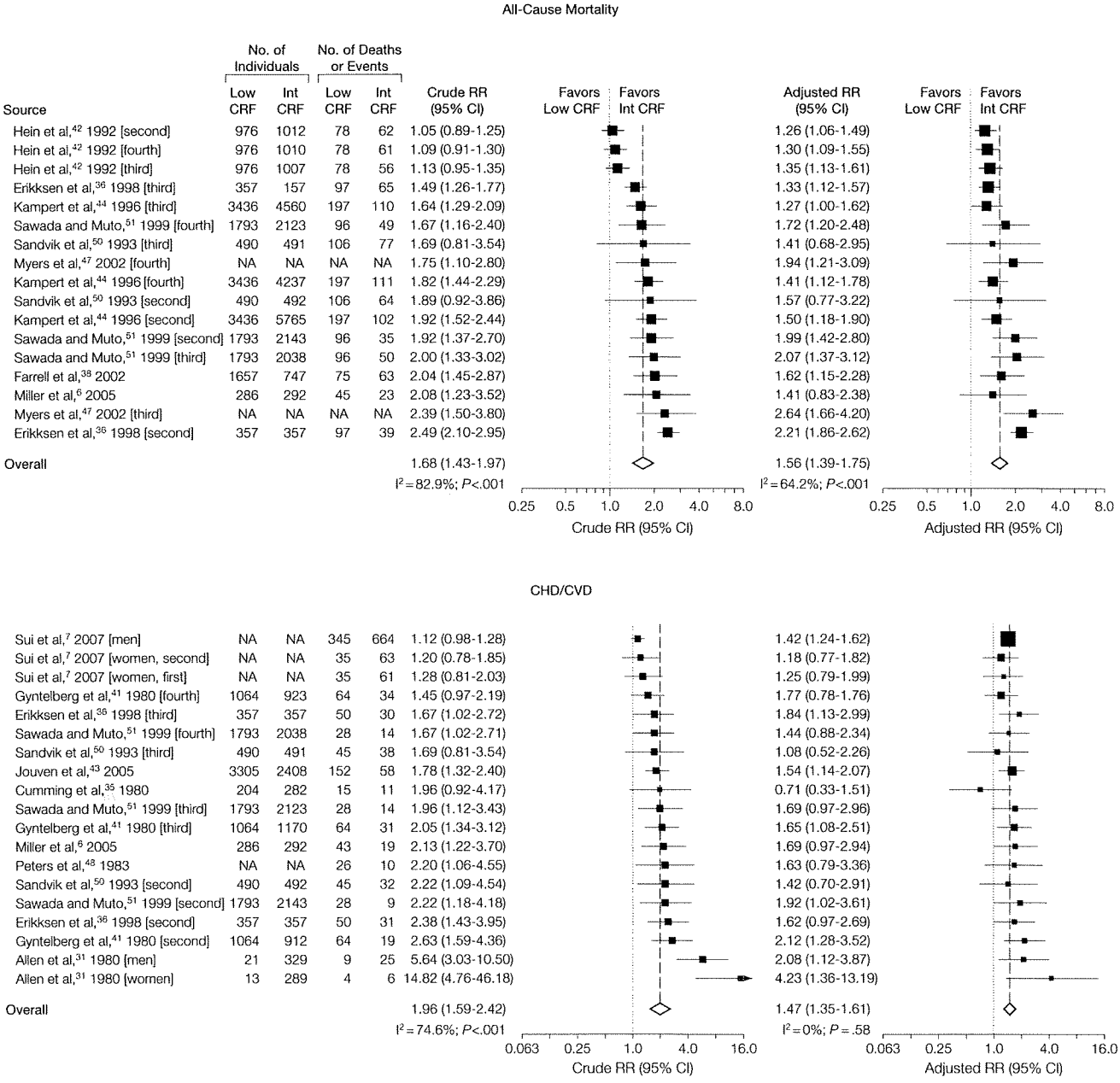


CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalent; NA, not available; RR, risk ratio. Low and high CRF categories were defined as less than 7.9 METs and 10.9 METs or more of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively.

cant risk reduction of all-cause mortality.[60] However, using CRF may be preferable to using physical activity as risk predictors because 1 prior study[61] suggested that physical fitness was more strongly correlated with CHD than physical activity.

According to the results reported herein, the minimum CRF level that is associated with significantly lower event rates for men and women is approximately 9 and 7 METs (at 40 years old), 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively. This means that women and men younger than 60 years

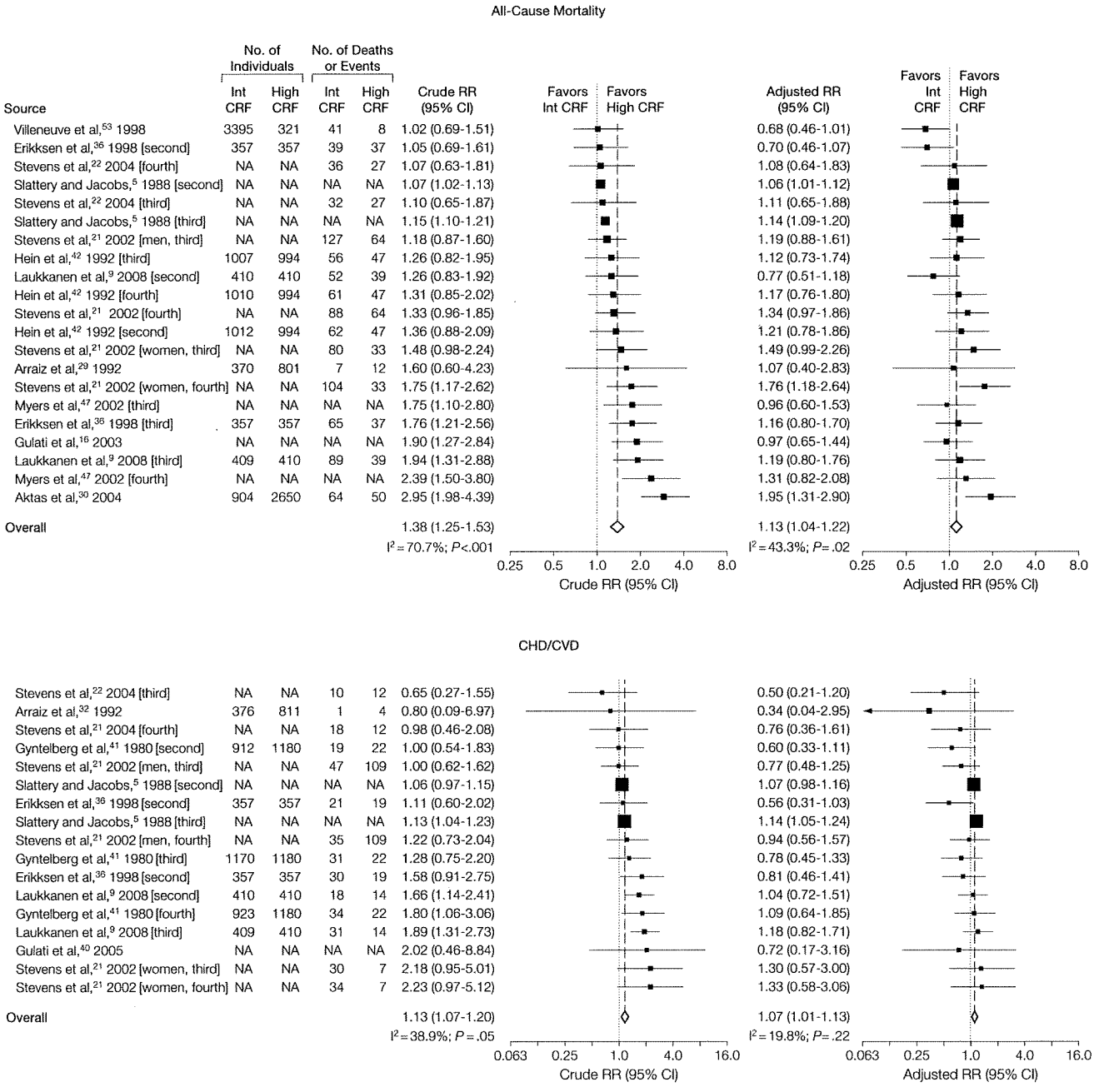
Figure 4. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Low vs Intermediate CRF



CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; Int, intermediate; MET, metabolic equivalent; NA, not available; RR, risk ratio. Low and intermediate CRF categories were defined as less than 7.9 METs and 7.9 to 10.8 METs of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively. The words first, second, third, and fourth in brackets represent comparisons between the lowest CRF category and the highest, second, third, or fourth CRF category in the relevant study.

would need to complete stage I (1.7 mph at gradient 10°) and stage II (2.5 mph at gradient 12°), respectively, of the standard Bruce protocol, which is one of the most commonly used treadmill tests in clinical settings.[14] If the CRF level is expressed in terms of walking speed, men around 50 years of age must be capable of continuous walking at a speed of 4 mph and women must continuously walk at 3 mph for prevention of CHD,[17] with the assumption that the anaerobic threshold is 50%

Figure 5. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Intermediate vs High CRF



CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; Int, intermediate; MET, metabolic equivalent; NA, not available; RR, risk ratio. Intermediate and high CRF categories were defined as 7.9 to 10.8 METs and 10.9 METs or more of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively. The words second, third, and fourth in brackets represent comparisons between the second, third, or fourth highest CRF category and the highest CRF category in the relevant study.

to 60% of MAC.[62] It is possible that consideration of low CRF as a major coronary risk factor could be put into practical use in the clinical setting through identification of low exercise tolerance by exercise stress testing or in daily life by the speed at which a person can walk before experiencing exhaustion.

Some cross-sectional population studies have suggested that higher aerobic fitness is associated with more favorable coronary or cardiovascular risk factor profiles[63,64]; therefore, the association between CRF and the risk of all-cause mortality and CHD/CVD could potentially be explained by residual confounding by established risk factors. Our sensitivity analyses indicated that a weaker association was observed between a 1-MET higher level of MAC and risk reduction of CHD/CVD, but not all-cause mortality, in studies with adjustment for smoking or more comprehensive risk factors. This finding suggests that better CRF is independently associated with longevity, while the inverse association between CRF and risk of CHD/CVD is explained partly by established coronary risk factors.

Limitations of this meta-analysis must be considered. First, a possible misclassification bias might affect our results. Misclassification bias could occur in transforming the reported CRF data into MET units. However, all of the prediction equations used in our analyses for estimating MAC have already been validated and are commonly used. Another possible misclassification bias is due to the fact that the definitions of low, intermediate, and high CRF were fundamentally based on study-specific CRF classifications, which varied from study to study but were not based on a standard cutoff. Fortunately, we could assign every exposure in each study to 1 of the 3 categories, which did not overlap with few exceptions, although MAC values in each category are approximately 1 MET smaller than those based on a general standard (eg, data from the National Health and Nutrition Examination Survey[65]). Therefore, the possibility of misclassification bias due to those 2 reasons should be limited. Second, Begg or Egger tests suggested publication bias. However, trim and fill analyses to incorporate potentially existing negative studies did not change the general result, although the risk estimates were moderately attenuated. Nevertheless, this possibility was not fully excluded by this analysis.

Based on the findings of our meta-analysis, we suggest for future research (1) further development of a CHD prediction algorithm (eg, Framingham Scores[66]) that would consider both CRF and the classical coronary risk factors to allow physicians to use CRF as a major risk factor in clinical settings; (2) cost-effectiveness of exercise testing for assessing CRF from the viewpoint of primary prevention of all-cause mortality and CHD; and (3) a clinical trial to determine whether an intervention that improves CRF by exercise reduces the risk of all-cause mortality and CHD.

In conclusion, better CRF was associated with lower risk of all-cause mortality and CHD/CVD. A 1-MET higher level of MAC was associated with a 13% and 15% risk reduction of all-cause mortality and CHD/CVD, respectively. The minimal MAC value for substantial risk reduction in persons aged 50 (SD, 10) years was estimated to be 8 (SD, 1) METs for men and 6 (SD, 1) METs for women. We suggest that CRF, which can be readily assessed by an exercise stress test, could be useful for prediction of CHD/CVD and all-cause mortality risk in a primary care medical practice.

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Acquisition of data: Kodama, Yachi, Sugawara, Totsuka.
Analysis and interpretation of data: Kodama, Tanaka, Asumi, Shimano, Ohashi, Yamada, Sone.
Drafting of the manuscript: Kodama, Maki, Sone.
Critical revision of the manuscript for important intellectual content: Kodama, Saito, Tanaka, Yachi, Asumi, Sugawara, Totsuka, Shimano, Ohashi, Yamada, Sone.
Statistical analysis: Kodama, Saito, Tanaka, Ohashi, Sone.
Obtained funding: Sone.
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Additional Information: The eTable is available at http://www.jama.com.

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