Jae, S. Y., Kurl, S., Kunutsor, S. K., & Laukkanen, J. (2021). Metabolic Syndrome, Cardiorespiratory Fitness and the Risk of All-cause and Cardiovascular Mortality in Men: A long-term prospective cohort study. *CardioMetabolic Syndrome Journal*, *1*(2), 157-165. https://doi.org/10.51789/cmsj.2021.1.e17

University of Bristol - Explore Bristol Research
General rights

CMSJ

Original Article

Check for updates

Correspondence to
Sae Young Jae, PhD
Health and Integrative Physiology Laboratory, Department of Sport Science, University of Seoul, 163 Seoulsiripdae-ro, Dongdaemun-gu, Seoul 02504, Korea.
E-mail: syjae@uos.ac.kr

ORCID iDs
Sae Young Jae
https://orcid.org/0000-0003-0358-7866
Setor K Kunutsor
https://orcid.org/0000-0002-2625-0273

Conflict of Interest
The authors have no financial conflicts of interest.

Metabolic Syndrome, Cardiorespiratory Fitness and the Risk of All-cause and Cardiovascular Mortality in Men: A Long-Term Prospective Cohort Study

Sae Young Jae ⓘD, PhD[1], Sudhir Kurl, MD[2], Setor K Kunutsor ⓘD, PhD[3,4], and Jari A. Laukkanen, MD[2]

[1]Health and Integrative Physiology Laboratory, Department of Sport Science, University of Seoul, Seoul, Korea
[2]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[3]National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK
[4]Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, UK

ABSTRACT

Background and Objectives: Cardiorespiratory fitness (CRF) ameliorates the increased risk of cardiovascular disease and mortality attributed to various risk factors. It is unclear whether the cardioprotective effects of CRF extend to attenuating the mortality risk associated with metabolic syndrome (MetS), which comprises a cluster of cardiometabolic risk factors. The purpose of this study was to examine the individual and joint associations of CRF and MetS with the risk of all-cause mortality and cardiovascular mortality.

Methods: This prospective study was based on a general population sample of 1,711 men in the Kuopio Ischemic Heart Disease cohort study. MetS was defined using the National Cholesterol Education Program criteria. CRF was directly measured as peak oxygen uptake during maximal exercise testing.

Results: During a median of 26 years follow-up, 799 all-cause mortality and 376 cardiovascular mortality events occurred. Men with MetS had a 41% increased risk of all-cause mortality and 76% increased risk of cardiovascular mortality in multivariable analysis, while men with upper levels of CRF demonstrated a 41% and 50% decreased risk of all-cause mortality and cardiovascular mortality, respectively, following adjustment for potential confounders. For the joint associations of MetS and CRF with the risk of outcomes, fit with MetS were at increased risks of death (all-cause mortality, hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.42–2.11; cardiovascular mortality, HR, 2.29; 95% CI, 1.71–3.07) compared with fit without MetS.

Conclusions: Although these results suggest that MetS and CRF were each independently associated with the risk of death, the latter did not eliminate the heightened risk of death associated with the former.

Keywords: Metabolic syndrome; Cardiorespiratory fitness; Mortality

Generated by xmlinkpress

CMSJ

Author Contributons

Conceptualization: Jae SY, Kunutsor SK, Laukkanen JA; Data curation: Kurl S, Laukkanen JA; Formal analysis: Kurl S, Kunutsor SK; Methodology: Kurl S, Kunutsor SK, Laukkanen JA; Visualization: Laukkanen JA; Writing - original draft: Jae SY; Writing - review & editing: Jae SY, Kurl S, Kunutsor SK, Laukkanen JA.

INTRODUCTION

Though several definitions exist, metabolic syndrome (MetS) is defined by a clustering of selected risk factors, including glucose intolerance, central obesity, high blood pressure, elevated serum triglycerides (TGs), and low high-density lipoprotein cholesterol (HDL-C).[1] The prevalence of MetS varies from 10 to 40%, or even higher, depending on the population and definition of MetS.[2,3] There is consistent evidence showing that MetS is associated with an increased risk of developing type 2 diabetes, cardiovascular disease (CVD) and mortality.[1,2]

Cardiorespiratory fitness (CRF) is a physiological biomarker of cardiopulmonary and muscular system integrity, that is reflective of physical activity behaviors.[4] Higher CRF levels are associated with a lower prevalence or incidence of MetS.[5] In addition, higher CRF levels are strongly associated with a lower risk of all-cause mortality (ACM) and cardiovascular mortality (CVM) in approximately healthy populations.[6,7] Furthermore, CRF is a more powerful predictor of CVD than traditional risk factors, while moderate to high levels of CRF has a protective or modifiable effect on mortality risk in individuals with specific disease or high-risk individuals, including those with obesity, smokers, hypertension, dyslipidemia, and diabetes.[8-11] These studies implicate the role of high CRF in attenuating or eliminating the detrimental effects of established risk factors. However, it remains unclear whether the cardioprotective effects of high CRF extend to attenuating the risk of death in individuals with MetS comprising a cluster of cardiometabolic risk factors.

Only 2 studies from the same group have suggested that high CRF attenuates the risk of all-cause and CVD mortality in men with MetS,[12,13] and thus, further studies are needed to confirm or refute these previous findings. Notably, an important limitation of these studies is that they did not use directly measured peak oxygen uptake (VO_{2peak}), the gold standard for assessing CRF,[14] and therefore, whether CRF measured as directly measured VO_{2peak}, attenuates MetS associated with mortality is not well documented and warrants further investigation.

We conducted a prospective study that examined the independent and joint associations of MetS and CRF with the risk of ACM and CVM in the general population. We hypothesized that both MetS and high CRF are associated with increased or decreased risk of these outcomes, respectively, but high CRF may attenuate or eliminate the increased risk associated with MetS.

METHODS

The Kuopio Ischemic Heart Disease (KIHD) study was designed to investigate risk factors for atherosclerotic cardiovascular outcomes and related health outcomes in a population-based sample of men. A sample of 3,235 (aged 42–60 years) eligible men who lived in the town of Kuopio or its surrounding area in eastern Finland were invited to partake in the study. Among those invited, 2,682 men participated in baseline examinations between 1984 and 1989. For the present analysis, we initially included 2,357 men who performed cardiopulmonary exercise testing and had available data on CRF. For the definition of the MetS, we excluded 646 participants who had missing data on waist girth (n=502) or biochemical values (n=144), leaving a sample of 1,711 men who had complete data on CRF and parameters of MetS at baseline. The study was approved by the Research Ethics Committee of the University of Eastern Finland (Kuopio, Finland) and all participants provided written informed consent.

Cardiorespiratory fitness

CRF was directly measured through peak oxygen consumption (mL/kg/min) during cardiopulmonary exercise testing to volitional fatigue/exhaustion. Peak oxygen uptake was defined as the highest attained value for oxygen consumption and classified by tertiles of CRF levels; lower (<26.7 mL/kg/min), middle (26.8–33.0 mL/kg/min), and upper (>33.1 mL/kg/min). CRF was also categorized by fit (middle and upper tertiles) and unfit (lower tertile) as previously described.[15]

MetS

MetS was determined based on the National Cholesterol Education Program (NCEP) criteria and the presence of MetS was defined as having three or more of the following risk factors: waist girth >102 cm, blood pressure >130/85 mm Hg or (hypertension), HDL-C <40 mg/dL (1.04 mmol/L), TGs >150 mg/dL (1.7 mmol/L), and glucose >100 mg/dL (5.6 mmol/L) or (diabetes).[16]

Other measurements

Resting blood pressure was measured 6 times (3 while supine, 1 while standing, and 2 while sitting) in the seated position and the mean of these values was used as resting blood pressure. Body mass index (BMI) was computed as the ratio of weight in kilograms (kg) to the square of height in meters (m). Waist circumference was calculated as the average of 2 measurements at the midpoint between the lowest rib and iliac crest. Assessment of smoking habits, presence of chronic diseases, and related demographic/lifestyle information (socioeconomic status, leisure-time physical activity and alcohol ingestion) were evaluated via a standardized self-administered questionnaire. The collection of blood samples, measurement of serum lipids, lipoproteins and glucose, and definitions of type 2 diabetes have been previously described.[17]

Ascertainment of outcomes

ACM and CVM were ascertained from hospital documents, discharge lists, death certificates, informant interviews, health practitioner questionnaires, study electrocardiograms, medico-legal reports and vital statistics offices. Deaths were coded using the tenth International Classification of Diseases codes. Documents were cross-checked in detail by 2 physicians.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (interquartile range; IQR) for continuous variables and proportions for categorical variables. Comparisons between baseline characteristics for participants with and without MetS were performed using a t-test and the χ^2 tests for continuous and categorical variables, respectively. To determine the associations between MetS (yes/no) and CRF (tertiles) with the risk of death, the hazard ratios (HRs) and 95% confidence intervals (95% CIs) from multivariable Cox proportional hazards regression models were calculated with adjustment for age, low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), cigarette smoking, alcohol consumption, leisure time physical activity, socioeconomic status (SES), family history of coronary heart disease (CHD), CVD history, and peak oxygen uptake. The joint effects of MetS and CRF on the risk of death were examined using four combined groups based on MetS and CRF (Fit-without MetS, Unfit-without MetS, Fit-with MetS, and Unfit-with MetS). The Fit-without MetS group was used as the reference comparison. Statistical significance was set at p<0.05, and analyses were conducted using the SPSS 25.0 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline characteristics of the participants overall and with and without MetS

Variables	Full cohort (n=1,711)	No MetS (n=1,143)	MetS (n=568)	p-value (No MetS vs. MetS)
Age (years)	52.5±5.6	52.1±5.7	53.2±5.5	<0.001
BMI (kg/m²)	26.9±3.4	25.7±2.7	29.2±3.6	<0.001
Waist girth (cm)	91.1±9.8	87.9±7.8	97.6±10.1	<0.001
Smokers (%)	30.9	33.3	26.1	0.002
Alcohol consumption/week g (JK)	32.3 (6.7–94.0)	32.0 (7.5–87.9)	32.7 (6.2–109.3)	0.491
SES*	9.0±4.5	8.8±4.6	9.4±4.4	0.008
Family history of coronary heart disease (%)	49.7	49.4	50.4	0.720
History of cardiovascular disease (%)	34.9	30.5	43.7	<0.001
Diabetes (%)	5.1	0.5	14.3	<0.001
Hypertension (%)	29.9	16.7	56.5	<0.001
Systolic blood pressure (mmHg)	133.0±16.5	128.2±15.2	142.7±14.6	<0.001
Diastolic blood pressure (mmHg)	88.5±10.5	85.2±9.7	95.2±8.9	<0.001
HDL-C (mmol/L)	1.29±0.3	1.35±0.3	1.16±0.3	<0.001
LDL-C (mmol/L)	3.96±0.9	3.95±1.0	3.99±0.9	<0.001
TGs (mmol/L)	1.31±0.8	1.06±0.5	1.80±1.1	<0.001
Glucose (mmol/L)	4.76±1.1	4.50±0.5	5.27±1.7	<0.001
CRP (mg/L)	1.23 (0.67–2.35)	1.03 (0.59–2.02)	1.67 (0.97–3.29)	<0.001
Leisure time physical activity (kcal/day)	291.7 (154.3–469.3)	296.1 (161.9–468.8)	287.7 (137.2–474.7)	0.382
Peak oxygen uptake (mL/kg/min)	30.7±8.1	32.6±7.8	26.8±7.0	<0.001

Data are shown as mean±standard deviation or median (interquartile range) and proportions.
CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; SES = socioeconomic status; TG = triglyceride.
*High score of the SES index indicates low SES.

RESULTS

Table 1 depicts the baseline characteristics of the participants overall and according to the presence and absence of MetS. Of the overall participants, 33.2% (n=568) were classified as having MetS. Participants with MetS were more likely to be older, have a history of CVD, diabetes, and hypertension, had higher levels of BMI, waist girth, systolic blood pressure, diastolic blood pressure, LDL-C, TG, glucose and CRP, and lower levels of SES, HDL-C, and VO$_{2peak}$ compared with participants without MetS (p<0.05 for all).

During a median of 26-year follow-up (IQR: 20–28 years), 799 ACM and 376 CVM events occurred, respectively. **Table 2** shows the risk of death for MetS and CRF. Compared with men without MetS, men with MetS demonstrated a 41% (HR, 1.41; 95% CI, 1.22–1.65) and 76% (HR, 1.76; 95% CI, 1.42–2.19) increased risk of ACM and CVM, respectively, after adjusting for age, LDL-C, CRP, cigarette smoking, alcohol consumption, leisure time physical activity, SES, family history of CHD, CVD history and peak oxygen uptake. Compared with the lower

Table 2. Associations of MetS and CRF with death

Variables	All-cause mortality	Cardiovascular mortality
MetS		
No	1 (reference)	1 (reference)
Yes	1.41 (1.22–1.65)	1.76 (1.42–2.19)
Cardiorespiratory fitness		
Lower (<26.7 mL/kg/min)	1 (reference)	1 (reference)
Moderate (26.8–33.0 mL/kg/min)	0.79 (0.67–0.94)	0.70 (0.55–0.89)
Upper (>33.1 mL/kg/min)	0.59 (0.48–0.72)	0.50 (0.37–0.68)

Values are presented as hazard ratio (95% confidence interval). Adjusted for age, LDL-C, CRP, cigarette smoking, alcohol consumption, leisure time physical activity, SES, family history of CHD, CVD history and peak oxygen uptake (when exposed MetS) or MetS (when exposed CRP).
CHD = coronary heart disease; CRF = cardiorespiratory fitness; CRP = C-reactive protein; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; SES = socioeconomic status.

Table 3. Joint associations of CRF and MetS with death

Variables	All-cause mortality	Cardiovascular mortality
Fit-without MetS	1 (reference)	1 (reference)
Unfit-without MetS	1.65 (1.34–2.02)	2.00 (1.48–2.73)
Fit-with MetS	1.73 (1.42–2.11)	2.29 (1.71–3.07)
Unfit-with MetS	2.00 (1.64–2.43)	2.92 (2.20–3.87)

Values are presented as hazard ratio (95% confidence interval). Adjusted for age, LDL-C, CRP, cigarette smoking, alcohol consumption, leisure time physical activity, SES, family history of CHD and CVD history. Fit (middle and upper tertiles) and unfit (lower tertile)
CHD = coronary heart disease; CRF = cardiorespiratory fitness; CRP = C-reactive protein; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; SES = socioeconomic status.

levels of CRF (<26.7 mg/kg/min), the upper levels of CRF (≥33.1 mg/kg/min) had significantly lower risks of ACM (HR, 0.59; 95% CI, 0.48–0.72) and CVD mortality (HR, 0.50; 95% CI, 0.37–0.68), after adjusting for confounders (**Table 2**).

For the joint associations of CRF and MetS with the risk of mortality (**Table 3**), the risks of mortality were increased in unfit with MetS (ACM: HR, 2.00; 95% CI, 1.64–2.43; CVM: HR, 2.92; 95% CI, 2.20–3.87) and unfit without MetS (ACM: HR, 1.65; 95% CI, 1.34–2.02; CVM: HR, 2.00; 95% CI, 1.48–2.73) compared with their fit without MetS counterparts (reference group) in multivariable analysis. In addition, the results for the risk of mortality showed a similar pattern in the fit with MetS group, where they were still at increased risk of death (ACM: HR, 1.73; 95% CI, 1.42–2.11; CVM: HR, 2.29; 95% CI, 1.71–3.07) compared with fit without MetS. The Kaplan–Meier curves demonstrated higher survival probability of all-cause and CVD mortality among males in the fit without MetS category compared with the other categories (p<0.001 for log-rank test) (**Figure 1**).

DISCUSSION

In this study, we sought to examine the independent associations of both MetS and CRF with the risk of mortality and whether high CRF may attenuate the increased risk of mortality associated MetS. Our findings revealed that MetS was significantly associated
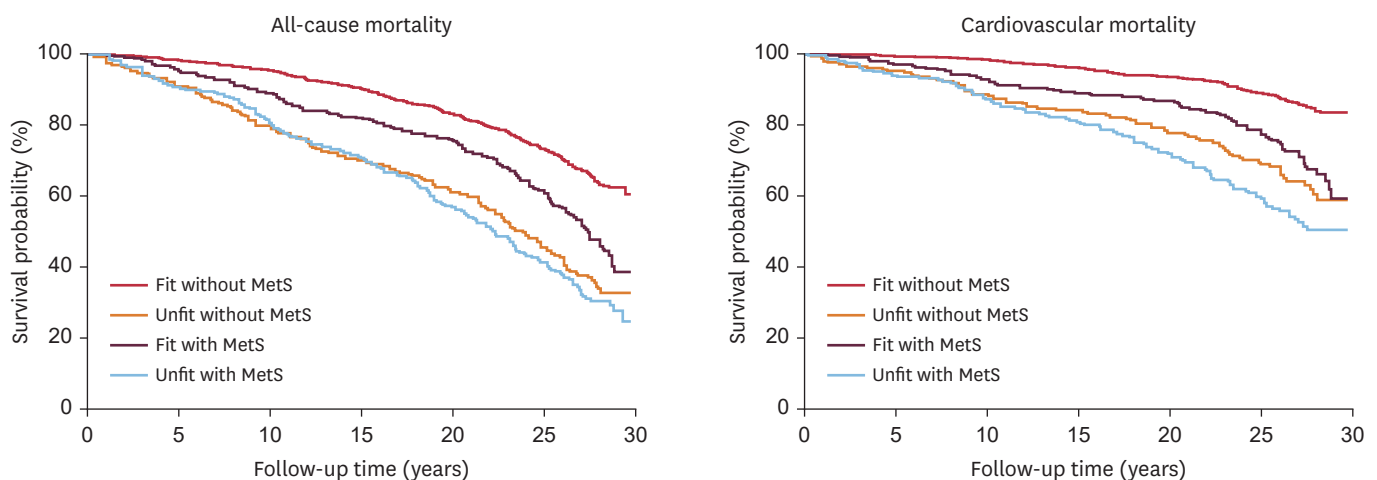
Figure 1. The Kaplan–Meier survival curves for all-cause and cardiovascular disease mortality by categories of the combination of cardiorespiratory fitness (Fit and Unfit) and MetS.
MetS = metabolic syndrome.

with an increased risk of ACM and CVD, independent of potential confounding variables, while moderate-to-upper levels of CRF were significantly associated with lower risk of these outcomes after adjusting for confounding factors. These findings are consistent with previous studies demonstrating that individuals with MetS have increased risk of death,[1] while CRF has been shown to be inversely associated with risk of death,[6,7,11] further extending the role of MetS and CRF as risk factors for mortality.

In this novel evaluation of the combined effects of MetS and objectively measured CRF on the risk of death in the present study, we found that both unfit with MetS and unfit without MetS were at the highest risk of death compared with fit without MetS. In addition, the heightened risk of death associated with MetS was not completely attenuated in fit people compared with fit without MetS. Thus, these findings suggest that the impact of MetS per se on the risk of ACM and CVD remains significant whether fit or not. Improving MetS represents a crucial therapeutic target that may ultimately confer a reduction in the risk of death associated with MetS in general populations, regardless of their CRF levels.

CRF has a protective effect in reducing ACM and CVM in healthy populations. Moreover, compared with obese unfit individuals, obese individuals with relatively good CRF levels appear to benefit from the associated cardioprotective adaptations. A meta-analysis demonstrated that the risk of all-cause mortality in overweight and obese individuals with low CRF was twice that of their normal weight with high CRF counterparts, but that mortality rates for overweight and obese individuals with high CRF were similar to those of normal-weight with high CRF individuals.[8] In addition, CRF appears to attenuate the risk of death associated with the presence of traditional risk factors, such as obesity, smoking, hypertension, dyslipidemia, and diabetes.[811] However, it remains unclear whether the cardioprotective effects of high CRF extend to attenuating the risk of death in individuals with MetS.

A few studies have explored the effect of physical activity on the heightened risk of ACM and CVM and increased risk for future CHD associated with MetS.[18-20] Previous studies have shown that moderate to vigorous physical activity appear to attenuate the risk of ACM and CVM in men and women with clustered metabolic risk factors.[18] In addition, physical activity at different intensities has attenuated cardiovascular events, ACM and CVM in men and women with MetS during a 20-year follow-up of a population-based cohort.[19] Another study suggested that individuals with MetS who were physically active had a lower CHD risk than people without MetS who were physically inactive.[20] However, these previous studies assessed leisure time physical activity using different self-report questionnaires, which may be susceptible to recall biases. Therefore, further clarification of the combined effects of objectively assessed physical activity and MetS on the risk of death is warranted.

CRF was regarded as a surrogate for habitual physical activity because the levels of CRF might be modified through decreasing or increasing of regular physical activity.[4] Interestingly, habitual physical activity is better represented by CRF than by self-reported physical activity, while directly CRF measured during maximal exercise test has been shown to be a stronger predictor of CVD outcomes then self-reported physical activity. Therefore, studies are needed to demonstrate whether moderate to high levels of CRF, a proxy of objectively measured physical activity levels, have a protective effect in attenuating ACM and CVM in populations with MetS. To best of our knowledge, only two studies have reported that high CRF attenuated the risk of ACM and CVM in men with MetS.[1,2,13] They reported that CRF provided a strong protective effect against ACM and CVM in healthy men and men with MetS.[12] In

another study from the same authors, MetS was associated with an increased risk of ACM and CVM, but these risks were largely explained by CRF.[13] These studies implicate the role of high CRF in attenuating the detrimental effects of MetS on the risk of death. However, this study did not use directly measured VO_{2peak}, an objective index of CRF, or adjust for baseline socioeconomic status, an important confounding variable.

In contrast to previous studies that showed that high levels of physical activity or estimated CRF from treadmill time attenuated the increased risk of ACM and CVM associated with MetS, the results in the present study demonstrated that moderate-to-upper levels of CRF did not completely eliminate the heightened risk of ACM and CVM associated with MetS. Methodological issues of CRF measurement, differences in definition of MetS, or age and sex differences between previous studies and the present study could be, in part, explain these conflicting results. In the present study, CRF was directly measured VO_{2peak}, which is a gold standard for assessing CRF and we used the NCEP criteria to define MetS in Caucasian men. Future studies are needed to confirm these results in participants with different racial or ethnic origins and women. Additionally, future studies are needed to clarify the associations of MetS and directly measured CRF with death risk.

The present study has several methodological limitations which should be acknowledged. Our study population included only Caucasian men, hence findings cannot be generalized to women and other races/ethnicities. CRF is not only determined by current physical activity level, but also by environmental and genetic factors; the proportion of fitness attributable to genetics is hypothesized as being relatively smaller than the proportion caused by physical activity. In addition, we classified CRF into unfit and fit categories based on VO_{2peak} percentiles; these categories may be viewed as somewhat arbitrary as there is currently a lack of such global CRF reference data. We used a single measurement of CRF at baseline and did not correct for serial changes in CRF over time or, for that matter, potential regression dilution bias. Although we adjusted for potential confounders to evaluate the independent associations of MetS and CRF and the risk of death, it is possible that residual variables that were not measured may have influenced the observed difference in relative risks. Despite these limitations, the strengths of this study included the long-term follow-up (prospective) and use of directly measured VO_{2peak}, which was not considered in previous studies.

In this population-based long-term prospective cohort study of men, our findings indicate that MetS and CRF were each independently associated with the risk of death, but the latter did not eliminate the heightened risk of death associated with the former. Thus, these findings suggest that the impact of MetS per se on the risk of ACM and CVD remains significant irrespective of CRF levels, which implies that MetS may be used as a therapeutic target to reduce the risk of death associated with MetS in general populations.

ACKNOWLEDGMENTS

REFERENCES

1. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.
   PUBMED | **CROSSREF**

2. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. JAMA 2015;313:1973-4.
   PUBMED | **CROSSREF**

3. Huh JH, Kang DR, Jang JY, et al. Metabolic syndrome epidemic among Korean adults: Korean survey of Cardiometabolic Syndrome (2018). Atherosclerosis 2018;277:47-52.
   PUBMED | **CROSSREF**

4. Laukkanen JA, Kunutsor SK. Fitness and reduced risk of hypertension-approaching causality. J Hum Hypertens. 2021 May 13 [Epub ahead of print]. https://doi.org/10.1038/s41371-021-00545-0.
   PUBMED | **CROSSREF**

5. Grundy SM, Barlow CE, Farrell SW, Vega GL, Haskell WL. Cardiorespiratory fitness and metabolic risk. Am J Cardiol 2012;109:988-93.
   PUBMED | **CROSSREF**

6. Jae SY, Kurl S, Kim HJ, et al. Is there an "Asymptote of Gain" beyond which further increases in cardiorespiratory fitness convey no additional benefits on mortality and atrial fibrillation? Mayo Clin Proc 2019;94:545-7.
   PUBMED | **CROSSREF**

7. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009;301:2024-35.
   PUBMED | **CROSSREF**

8. Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause mortality: a meta-analysis. Prog Cardiovasc Dis 2014;56:382-90.
   PUBMED | **CROSSREF**

9. Jae SY, Franklin BA, Kurl S, et al. Effect of cardiorespiratory fitness on risk of sudden cardiac death in overweight/obese men aged 42 to 60 years. Am J Cardiol 2018;122:775-9.
   PUBMED | **CROSSREF**

10. Farrell SW, Finley CE, Barlow CE, et al. Moderate to high levels of cardiorespiratory fitness attenuate the effects of triglyceride to high-density lipoprotein cholesterol ratio on coronary heart disease mortality in men. Mayo Clin Proc 2017;92:1763-71.
    PUBMED | **CROSSREF**

11. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.
    PUBMED | **CROSSREF**

12. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092-7.
    PUBMED | **CROSSREF**

13. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care 2005;28:391-7.
    PUBMED | **CROSSREF**

14. Ozemek C, Laddu DR, Lavie CJ, et al. An update on the role of cardiorespiratory fitness, structured exercise and lifestyle physical activity in preventing cardiovascular disease and health risk. Prog Cardiovasc Dis 2018;61:484-90.
    PUBMED | **CROSSREF**

15. McAuley PA, Artero EG, Sui X, Lavie CJ, Almeida MJ, Blair SN. Fitness, fatness, and survival in adults with prediabetes. Diabetes Care 2014;37:529-36.
    PUBMED | **CROSSREF**

16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
    PUBMED | **CROSSREF**

17. Kurl S, Laaksonen DE, Jae SY, et al. Metabolic syndrome and the risk of sudden cardiac death in middle-aged men. Int J Cardiol 2016;203:792-7.
    PUBMED | **CROSSREF**

18. Hamer M, Stamatakis E. Low-dose physical activity attenuates cardiovascular disease mortality in men and women with clustered metabolic risk factors. Circ Cardiovasc Qual Outcomes 2012;5:494-9.
PUBMED | CROSSREF

19. Ekblom-Bak E, Halldin M, Vikström M, et al. Physical activity attenuates cardiovascular risk and mortality in men and women with and without the metabolic syndrome - a 20-year follow-up of a population-based cohort of 60-year-olds. Eur J Prev Cardiol 2020 Apr 10 [Epub ahead of print]. https://doi.org/10.1177/2047487320916596.
PUBMED | CROSSREF

20. Broekhuizen LN, Boekholdt SM, Arsenault BJ, et al. Physical activity, metabolic syndrome, and coronary risk: the EPIC-Norfolk prospective population study. Eur J Cardiovasc Prev Rehabil 2011;18:209-17.
PUBMED | CROSSREF