**Table 1** Baseline characteristics of study participants by physical activity categories, Aerobics Center Longitudinal Study, 1970–2003

| | Physical activity categories | | | |
|---|---|---|---|---|
| | Sedentary | Walker/jogger/runner | Sport/fitness | p Value |
| N | 7158 | 11 478 | 4808 | |
| Age (mean±SD, years) | 44.7±9.7 | 44.9±9.8 | 45.5±9.9 | <0.0001 |
| Body mass index (mean±SD, kg/m$^2$) | 26.7±3.8 | 25.7±3.3 | 26.4±3.7 | <0.0001 |
| Exercise tolerance (mean±SD, maximal metabolic equivalents achieved during the treadmill test) | 10.4±2.0 | 12.7±2.5 | 11.5±2.2 | <0.0001 |
| Treadmill test duration (mean±SD, min) | 15.2±4.2 | 20.1±4.8 | 17.6±4.5 | <0.0001 |
| Lipids (mean±SD, mg/dl) | | | | |
| Total cholesterol | 216.1±39.9 | 204.6±37.8 | 206.9±38.8 | <0.0001 |
| High-density lipoprotein cholesterol | 43.8±11.4 | 47.6±12.2 | 46.2±11.9 | <0.0001 |
| Triglycerides | 147.8±107.6 | 119.5±82.1 | 134.1± 107.0 | <0.0001 |
| Fasting blood glucose (mean±SD, mg/dl) | 99.6±10.0 | 98.2±9.2 | 98.2±9.1 | <0.0001 |
| Blood pressure (mean±SD, mm Hg) | | | | |
| Systolic | 123±14 | 122±14 | 121±13 | <0.0001 |
| Diastolic | 82±10 | 81±9 | 81±9 | <0.0001 |
| Smoking status (%) | | | | <0.0001 |
| Never smoker | 50.9 | 52.5 | 53.9 | |
| Past smoker | 27.4 | 36.8 | 29.8 | |
| Current smoker | 21.7 | 10.8 | 16.4 | |
| Alcohol consumption (mean±SD, drinks/week) | 8.4±11.8 | 7.9±12.5 | 8.1±12.6 | 0.12 |
| Hypercholesterolaemia (%) | 24.4 | 15.5 | 17.4 | <0.0001 |
| Hypertension (%) | 33.9 | 29.6 | 30.7 | <0.0001 |
| Family history of diabetes (%) | 4.3 | 6.2 | 7.1 | <0.0001 |
| Family history of cardiovascular disease (%) | 3.7 | 5.5 | 5.5 | <0.0001 |

SI conversion factors: to convert total cholesterol and high-density lipoprotein cholesterol values to mmol/l, multiply by 0.0259; triglycerides values to mmol/l, by 0.0113; glucose values to mmol/l, by 0.0555.

**Table 2** Baseline characteristics of study participants by cardiorespiratory fitness categories, Aerobics Center Longitudinal Study, 1970–2003

| | Cardiorespiratory fitness categories | | | |
|---|---|---|---|---|
| | Low | Moderate | High | p Value |
| N | 3301 | 9101 | 11042 | |
| Age (mean±SD, years) | 44.2±9.5 | 45.0±9.6 | 45.1±9.9 | <0.0001 |
| Body mass index (mean±SD, kg/m$^2$) | 28.8±5.0 | 26.6±3.3 | 24.9±2.6 | <0.0001 |
| Exercise tolerance (mean±SD, maximal metabolic equivalents achieved during the treadmill test) | 8.5±1.3 | 10.7±1.2 | 13.6±2.0 | <0.0001 |
| Treadmill test duration (mean±SD, min) | 11.2±2.7 | 15.9±2.5 | 22.1±3.6 | <0.0001 |
| Lipids (mean±SD, mg/dl) | | | | |
| Total cholesterol | 218.5±41.2 | 212.1±39.0 | 202.6±37.3 | <0.0001 |
| High-density lipoprotein cholesterol | 40.9±10.8 | 44.0±11.0 | 49.3±12.2 | <0.0001 |
| Triglycerides | 176.3±129.0 | 144.2 ±104.5 | 106.6±66.7 | <0.0001 |
| Fasting blood glucose (mean±SD, mg/dl) | 100.3±10.1 | 99.1± 9.6 | 97.7±8.9 | <0.0001 |
| Blood pressure (mean±SD, mm Hg) | | | | |
| Systolic | 125±15 | 122±13 | 121±13 | <0.0001 |
| Diastolic | 84±10 | 82±10 | 80±9 | <0.0001 |
| Physical activity (%) | | | | <0.0001 |
| Sedentary | 63.9 | 40.2 | 12.6 | |
| Walker/jogger/runner | 19.1 | 36.2 | 68.4 | |
| Sport/fitness | 17.0 | 23.6 | 19.0 | |
| Smoking status (%) | | | | <0.0001 |
| Never smoker | 40.8 | 50.0 | 57.6 | |
| Past smoker | 31.0 | 32.0 | 33.3 | |
| Current smoker | 28.3 | 18.0 | 9.2 | |
| Alcohol consumption (mean±SD, drinks/week) | 8.8±12.3 | 8.4±12.6 | 7.6±12.1 | <0.0001 |
| Hypercholesterolaemia (%) | 26.9 | 21.2 | 14.1 | <0.0001 |
| Hypertension (%) | 44.0 | 33.5 | 25.3 | <0.0001 |
| Family history of diabetes (%) | 4.5 | 5.9 | 6.1 | <0.003 |
| Family history of cardiovascular disease (%) | 3.9 | 4.5 | 5.6 | <0.0001 |

SI conversion factors: To convert total cholesterol and high-density lipoprotein cholesterol values to mmol/l, multiply by 0.0259; triglycerides values to mmol/l, by 0.0113; glucose values to mmol/l, by 0.0555.

**Table 3** Hazard ratios (HR) for developing diabetes, according to baseline physical activity and cardiorespiratory fitness category

| | Cases | Man-years | Rate* | Model 1† HR (95% CI) | Model 2‡ HR (95% CI) | Model 3§ HR (95% CI) |
|---|---|---|---|---|---|---|
| Physical activity | | | | | | |
| Sedentary | 300 | 152 680 | 20.1 | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| Walker/jogger/runner | 195 | 198 569 | 9.6 | 0.44 (0.37 to 0.53) | 0.60 (0.48 to 0.74) | 0.76 (0.60 to 0.96) |
| Sport/fitness | 94 | 73 178 | 12.4 | 0.60 (0.47 to 0.76) | 0.72 (0.55 to 0.94) | 0.81 (0.62 to 1.07) |
| Cardiorespiratory fitness | | | | | | |
| Low | 214 | 69 387 | 31.9 | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| Moderate | 250 | 170 553 | 14.5 | 0.42 (0.35 to 0.51) | 0.62 (0.49 to 0.78) | 0.65 (0.51 to 0.82) |
| High | 125 | 184 401 | 6.5 | 0.18 (0.14 to 0.23) | 0.37 (0.28 to 0.50) | 0.43 (0.31 to 0.60) |
| p Value for linear trend | | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

*Rate per 10 000 man-years adjusted for age and examination year.
†Model 1: adjusted for baseline age, examination year and survey response pattern.
‡Model 2: adjusted for all variables in Model 1 plus body mass index (kg/m$^2$), smoking status (never, former and current), alcohol intake (drinks per week), fasting glucose (mg/dl), hypercholesterolaemia (yes or no), hypertension (yes or not), family history of diabetes (present or not) and family history of cardiovascular disease (present or not).
§Model 3: adjusted for all variables in Model 2 plus physical activity or cardiorespiratory fitness.

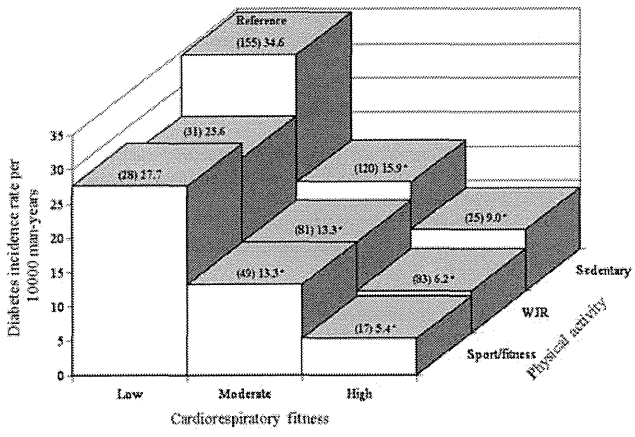


**Figure 1** Total number of cases (N) and age- and examination year-adjusted diabetes incidence rates per 10 000 man-years according to cardiorespiratory fitness (CRF) and physical activity (PA) categories. The adjusted incidence rate was inversely related to CRF within each of the PA groups (all p<0.0001 for trend); however, there was no association between walking/jogging/running or sport/fitness activity group and outcome within any of the fitness groups, compared with the sedentary men (all p>0.05). *Significant difference compared with the reference.

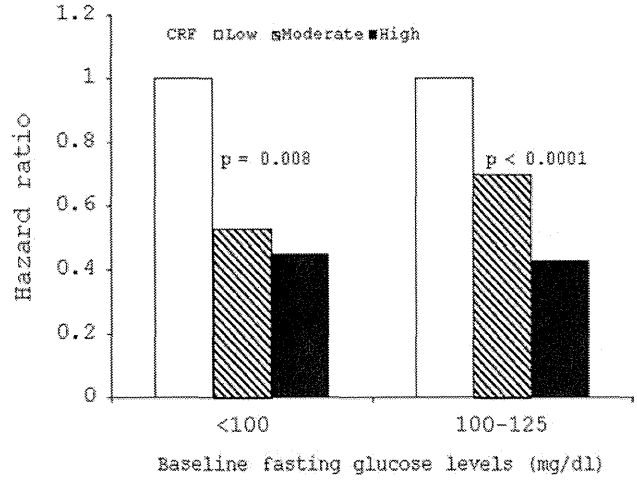


**Figure 2** Multivariate-adjusted hazard ratios for cardiorespiratory fitness (CRF) and incident diabetes by baseline glucose levels. The height of bars represent HRs adjusted for age, examination year, body mass index (kg/m$^2$), smoking status (never, former and current), alcohol intake (drinks per week), fasting glucose (mg/dl), hypercholesterolaemia (yes or no), hypertension (yes or not), family history of diabetes (present or not), family history of cardiovascular disease (present or not) and physical activity.

found that physical fitness, not PA, was an important predictor independent of other risk factors. They explained that some of the discrepant results for the influence of PA may be related to the measures of PA versus physical fitness.[16] We found that both PA and fitness affected incidence diabetes, even after adjusting for each other. Some of the possible explanations about the different findings from PALS are as follows. They modelled their questionnaire after the Minnesota Leisure Time PA questionnaire, which collects information over the previous 12 months. In our study, we only collected activity data over the previous 3 months. PALS calculated the average daily leisure-time activity energy expenditure; however, we have no such data available. Insufficient sample size in PALS and differences in population age may also play a role.

The effect of CRF or PA on incident diabetes may be explained by several pathways. Upregulation of glucose from enhanced skeletal muscle mitochondria enzyme activity may be the contributor enhanced in those participating in PA. Decrease in insulin resistance and increase in insulin sensitivity[44] of skeletal muscle may be due to increased activity for physical demands. Although CRF has a genetic component (25–40%),[45 46] it is clear that usual PA habits are the primary determinant of fitness. In the current study, PA and CRF were only weakly associated (r=0.26). Finally, greater activity may improve one's concurrent conditions such as hypertension, dyslipidaemia and abdominal obesity, where the body is reacting to chronic systemic inflammation.[3]

Strengths of this study include the extensive baseline examination, the large size of the cohort, the long follow-up period and the objective laboratory treadmill testing for quantifying CRF. There are several limitations that need to be considered

when interpreting these data. Recall bias might lead to the misclassification of the PA groups. In terms of exposure assessment, we classified men at study enrolment, but in the present analysis, we were unable to evaluate the effect of changes in PA and fitness over time on our diabetes outcomes. It is possible that sedentary or low-fitness men increased their activity or fitness levels at some point in the follow-up interval. Additionally, others may have experienced decreases in these characteristics. Such misclassification of exposure would likely underestimate the magnitude of the association observed in the present study. Other risk factors might also change during the long period of follow-up. Most of the men were white and from middle-to-upper socio-economic strata, which may limit the generalizability but should not affect the internal validity. Furthermore, the activity intensity of the WJR group and sports/fitness groups was not distinguished. We have no data from the oral glucose tolerance test (OGTT). It is likely that OGTT would have identified some of the men as having diabetes at baseline, and this could have influenced the results. Since we are only counting those diagnosed as having diabetes from the returned surveys, it is possible that those undiagnosed cases may be misclassified. However, our methods of case ascertainment should not be less valid than those of other epidemiological studies[16 38 39] in which self-reported diabetes were used. Finally, there is no sufficient diet or medication information available to include in the analysis.

## CONCLUSION

In conclusion, our prospective findings show a lower risk of developing diabetes if men participated in WJR or some type of sport activity rather than being sedentary. CRF had a strong inverse association with incident diabetes. The joint association of either WJR or sport/fitness combined with a high level of CRF provided the higher protective influence on type 2 diabetes, compared with a sedentary lifestyle. Even with overwhelming evidence that it is important to stay physically active and to improve CRF, less than 40% of adults with diabetes reported being regularly engaged in moderate or vigorous PA.[12] Therefore, health professionals should actively advise the general public as well as people with diabetes to lead an active lifestyle and improve their fitness level.

### What is already known on this topic

- Although the independent effects of physical activity or cardiorespiratory fitness on incident diabetes are well established, additional studies are needed on the combined association and relative contributions of physical activity and fitness to diabetes prevention.

### What this study adds

- Being active and fit provided a higher protective influence on type 2 diabetes. The much stronger inverse association for fitness compared with activity suggests that earlier studies on activity and diabetes may have underestimated the true association. We hope our findings will encourage health professionals to promote physical activity and actively advise all patients to improve their fitness level.

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**Competing interests** None.

**Ethics approval** Ethics approval was provided by the The Cooper Institute IRB.

**Provenance and peer review** Not commissioned; externally peer reviewed.

Detail has been removed from these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

## REFERENCES

1. **Cowie CC**, Rust KF, Byrd-Holt DD, *et al.* Prevalence of diabetes and impaired fasting glucose in adults in the US population: National Health And Nutrition Examination Survey 1999–2002. *Diabetes Care* 2006;**29**:1263–8.
2. Economic costs of diabetes in the US In 2007. *Diabetes Care* 2008;**31**:596–615.
3. **LaMonte MJ**, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol* 2005;**99**:1205–13.
4. **Sigal RJ**, Kenny GP, Wasserman DH, *et al.* Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006;**29**:1433–8.
5. **Bassuk SS**, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol* 2005;**99**:1193–204.
6. **Jeon CY**, Lokken RP, Hu FB, *et al.* Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care* 2007;**30**:744–52.
7. **Williams PT**. Vigorous exercise, fitness and incident hypertension, high cholesterol, and diabetes. *Med Sci Sports Exerc* 2008;**40**:998–1006.
8. **Wei M**, Gibbons LW, Mitchell TL, *et al.* The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 1999;**130**:89–96.
9. **Wareham NJ**, Wong MY, Day NE. Glucose intolerance and physical inactivity: the relative importance of low habitual energy expenditure and cardiorespiratory fitness. *Am J Epidemiol* 2000;**152**:132–9.
10. **Hu G**, Lakka TA, Barengo NC, *et al.* Physical activity, physical fitness, and risk of type 2 diabetes mellitus. *Metab Syndr Relat Disord* 2005;**3**:35–44.
11. **Okada K**, Hayashi T, Tsumura K, *et al.* Leisure-time physical activity at weekends and the risk of Type 2 diabetes mellitus in Japanese men: the Osaka Health Survey. *Diabet Med* 2000;**17**:53–8.
12. **Morrato EH**, Hill JO, Wyatt HR, *et al.* Physical activity in US adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care* 2007;**30**:203–9.
13. **Telford RD**. Low physical activity and obesity: causes of chronic disease or simply predictors? *Med Sci Sports Exerc* 2007;**39**:1233–40.
14. **Laaksonen DE**, Lindström J, Lakka TA, *et al.* Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 2005;**54**:158–65.
15. **Sui X**, Hooker SP, Lee IM, *et al.* A prospective study of cardiorespiratory fitness and risk of type 2 diabetes in women. *Diabetes Care* 2008;**31**:550–5.
16. **Katzmarzyk PT**, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: the physical activity longitudinal study. *Diabetologia* 2007;**50**:538–44.
17. **Wei M**, Schwertner HA, Blair SN. The association between physical activity, physical fitness, and type 2 diabetes mellitus. *Compr Ther* 2000;**26**:176–82.
18. **Buse JB**, Ginsberg HN, Bakris GL, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007;**30**:162–72.
19. US Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. http://www.health.gov/paguidelines/guidelines/default.aspx. Accessed 14 March 2009.
20. **Esliger DW**, Tremblay MS. Physical activity and inactivity profiling: the next generation. *Can J Public Health* 2007;**98** (Suppl 2):S195–207.
21. **Shephard RJ**. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* 2003;**37**:197–206.

22. **Aadahl M**, Kjaer M, Kristensen JH, *et al.* Self-reported physical activity compared with maximal oxygen uptake in adults. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:422–8.
23. **Tudor-Locke CE**, Myers AM. Challenges and opportunities for measuring physical activity in sedentary adults. *Sports Med* 2001;**31**:91–100.
24. **LaPorte RE**, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Rep* 1985;**100**:131–46.
25. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 1998;**30**:975–91.
26. **Haskell WL**, Leon AS, Caspersen CJ, *et al.* Cardiovascular benefits and assessment of physical activity and physical fitness in adults. *Med Sci Sports Exerc* 1992;**24**:S201–20.
27. **Lynch J**, Helmrich SP, Lakka TA, *et al.* Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 1996;**156**:1307–14.
28. **Blair SN**, Kohl HW 3rd, Paffenbarger RS Jr, *et al.* Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989;**262**:2395–401.
29. **Blair SN**, Kampert JB, Kohl HW 3rd, *et al.* Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996;**276**:205–10.
30. **Pickering TG**, Hall JE, Appel LJ, *et al.* Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;**45**:142–61.
31. **Hootman JM**, Macera CA, Ainsworth BE, *et al.* Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. *Am J Epidemiol* 2001;**154**:251–8.
32. **Hootman JM**, Macera CA, Ainsworth BE, *et al.* Epidemiology of musculoskeletal injuries among sedentary and physically active adults. *Med Sci Sports Exerc* 2002;**34**:838–44.
33. **Balke B**, Ware RW. An experimental study of physical fitness of Air Force personnel. *U S Armed Forces Med J* 1959;**10**:675–88.
34. **Pollock ML**, Bohannon RL, Cooper KH, *et al.* A comparative analysis of four protocols for maximal treadmill stress testing. *Am Heart J* 1976;**92**:39–46.
35. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th edn. Philadelphia, Pennsylvania, USA: Lippincott Williams & Wilkins, 2000.
36. **Macera CA**, Jackson KL, Davis DR, *et al.* Patterns of non-response to a mail survey. *J Clin Epidemiol* 1990;**43**:1427–30.
37. **Wei M**, Gibbons LW, Mitchell TL, *et al.* Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* 2000;**23**:18–22.
38. **Weinstein AR**, Sesso HD, Lee IM, *et al.* Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA* 2004;**292**:1188–94.
39. **Sawada SS**, Lee IM, Muto T, *et al.* Cardiorespiratory fitness and the incidence of type 2 diabetes: prospective study of Japanese men. *Diabetes Care* 2003;**26**:2918–22.
40. Centers for Disease Control and Prevention. National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/pdf/ndfs _ 2007.pdf. Accessed 5 May 2009.
41. **Barlow CE**, LaMonte MJ, Fitzgerald SJ, *et al.* Cardiorespiratory fitness is an independent predictor of hypertension incidence among initially normotensive healthy women. *Am J Epidemiol* 2006;**163**:142–50.
42. **Lee DC**, Sui X, Church TS, *et al.* Associations of cardiorespiratory fitness and obesity with risks of impaired fasting glucose and type 2 diabetes in men. *Diabetes Care* 2009;**32**:257–62.
43. **Church TS**, Earnest CP, Skinner JS, *et al.* Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA* 2007;**297**:2081–91.
44. **Toledo FG**, Menshikova EV, Ritov VB, *et al.* Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. *Diabetes* 2007;**56**:2142–7.
45. **Bouchard C**, Daw EW, Rice T, *et al.* Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc* 1998;**30**:252–8.
46. **Bouchard C**, An P, Rice T, *et al.* Familial aggregation of VO (2max) response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol* 1999;**87**:1003–8.

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|---|---|
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| 著 者 | Sieverdes JC, Sui X, Lee DC, Church TS, McClain A, Hand GA, Blair SN. |
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| 巻・号・頁 | 44(4) 238-244 |
| 発行年 | 2010 |
| PubMedリンク | http://www.ncbi.nlm.nih.gov/pubmed/19656767 |

| 対象の内訳 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | ヒト | 動物 | | 欧米 | | 縦断研究 |
| 対象 | 一般健常者 | 空白 | | ( ) | | コホート研究 |
| 性別 | 男性 | ( ) | 地 域 | ( ) | 研究の種類 | ( ) |
| 年齢 | 20-85歳 | [redacted] | | ( ) | | 前向きコホート |
| 対象数 | 10000以上 | | | ( ) | | ( ) |
| 調査の方法 | 実測 | ( 質問紙 ) | | | | |
| アウトカム | | | | | | |
| 予 防 | なし | 糖尿病予防 | なし | なし | | ( ) |
| 維持・改善 | な し | な し | な し | なし | ( | ( ) |

**図 表**

Table 3 Hazard ratios (HR) for developing diabetes, according to baseline physical activity and cardiorespiratory fitness category

| | Cases | Man-years | Rate* | Model 1† HR (95% CI) | Model 2‡ HR (95% CI) | Model 3§ HR (95% CI) |
|---|---|---|---|---|---|---|
| Physical activity | | | | | | |
| Sedentary | 300 | 152 680 | 20.1 | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| Walker/jogger/runner | 195 | 198 569 | 9.6 | 0.44 (0.37 to 0.53) | 0.60 (0.48 to 0.74) | 0.76 (0.60 to 0.96) |
| Sport/fitness | 94 | 73 178 | 12.4 | 0.60 (0.47 to 0.76) | 0.72 (0.55 to 0.94) | 0.81 (0.62 to 1.07) |
| Cardiorespiratory fitness | | | | | | |
| Low | 214 | 69 387 | 31.9 | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| Moderate | 250 | 170 553 | 14.5 | 0.42 (0.35 to 0.51) | 0.62 (0.49 to 0.78) | 0.65 (0.51 to 0.82) |
| High | 125 | 184 401 | 6.5 | 0.18 (0.14 to 0.23) | 0.37 (0.28 to 0.50) | 0.43 (0.31 to 0.60) |
| p Value for linear trend | | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

*Rate per 10 000 man-years adjusted for age and examination year.
†Model 1: adjusted for baseline age, examination year and survey response pattern.
‡Model 2: adjusted for all variables in Model 1 plus body mass index (kg/m$^2$), smoking status (never, former and current), alcohol intake (drinks per week), fasting glucose (mg/dl), hypercholesterolaemia (yes or no), hypertension (yes or not), family history of diabetes (present or not) and family history of cardiovascular disease (present or not).
§Model 3: adjusted for all variables in Model 2 plus physical activity or cardiorespiratory fitness.

| | |
|---|---|
| 図表掲載箇所 | P242, 表3 |
| 概 要 (800字まで) | 本研究は，身体活動および全身持久力と2型糖尿病発症との関連について検討したエアロビクスセンターの縦断研究(ACLS)である．ベースラインにおいて心血管疾患，癌，糖尿病でない23444名の男性を対象とし，平均18年間観察された．全身持久力は，修正版Balkeトレッドミルプロトコルによって評価された．年齢特異的な分布を考慮し，低体力：下位20%(8.5メッツ)，中体力：次の40%(10.7メッツ)，高体力：最も高い40%(13.6メッツ)の3つにカテゴリー化し，解析された．身体活動は，過去3か月間の活動について質問され，不活動群，ウォーキング・ジョギング・ランニング活動群，スポーツ活動群の3つに分類された．全身持久力が最も低い群と比較して，中体力群の糖尿病発症における調整ハザード比は0.65(95%CI:0.51-0.82)，高体力群では0.43(0.31-0.60)であり，全身持久力が高いものは糖尿病発症リスクが低いことが示された．また，身体活動に関しては，不活動の者と比較して，ウォーキング・ジョギング・ランニング活動群の調整ハザード比は0.76(0.60-0.96)，スポーツ活動群では0.81(0.62-1.07)であった． |
| 結 論 (200字まで) | 全身持久力が高い者は，低い者よりも身体活動量で補正しても糖尿病発症リスクが低い．ウォーキング，ジョギング，ランニングまたはスポーツ活動を行っている者は，不活動の者よりも糖尿病発症リスクが低い． |
| エキスパートによるコメント (200字まで) | アメリカのエアロビクスセンターで行われた大規模なコホート研究により，全身持久力と2型糖尿病発症リスクとの関連について明らかにしたものであり，全身持久力を高めるような有酸素運動を推奨する上で重要なエビデンスのひとつである． |

担当者 川上諒子

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PAPER

# Associations of fitness and fatness with mortality in Russian and American men in the lipids research clinics study

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**OBEJECTIVE:** To examine the relative size of the effects of fitness and fatness on mortality in Russian men, and to make comparison to US men.
**DESIGN:** Prospective closed cohort.
**SUBJECTS:** 1359 Russian men and 1716 US men aged 40–59 y at baseline (1972–1977) who were enrolled in the Lipids Research Clinics Study.
**MEASUREMENTS:** Fitness was assessed using a treadmill test and fatness was assessed as body mass index (BMI) calculated from measured height and weight. Hazard ratios were calculated using proportional hazard models that included covariates for age, education, smoking, alcohol intake and dietary keys score. All-cause and cardiovascular disease (CVD) mortality were assessed through 1995.
**RESULTS:** In Russian men, fitness was associated with all-cause and CVD mortality, but fatness was not. For mortality from all causes, compared to the fit-not fat, the adjusted hazard ratios were 0.87 (95% CI: 0.55, 1.37) among the fit-fat, 1.86 (95% CI: 1.31, 2.62) among the unfit-not fat and 1.68 (95% CI: 1.06, 2.68) among the unfit-fat. Among US men, the same hazard ratios were 1.40 (95% CI: 1.07, 1.83), 1.41 (95% CI: 1.12, 1.77) and 1.54 (95% CI: 1.24, 2.06), respectively. There were no statistically significant interactions between fitness and fatness in either group of men for all-cause or CVD mortality.
**CONCLUSION:** The effects of fitness on mortality may be more robust across populations than are the effects of fatness.
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**Keywords:** cardiorespiratory fitness; epidemiology; international; longevity; physical activity; Russia; survival analysis

## Introduction

Reports from the Aerobics Center Longitudinal Study have examined the independent and combined effects of fatness and fitness on all-cause and cardiovascular disease (CVD) mortality in men[1–6] and in women.[2,7] These studies examined clients who received medical examinations at the Cooper Institute for Aerobics Research in Dallas, Texas[2] and who were predominantly white, college graduates. The reports from the Aerobics Center Longitudinal Study presented some evidence that fitness was a more potent risk factor for mortality than was fatness. Recently, we reported an analysis of data from a cohort of US women and men drawn from diverse geographic locations examining the inter-related effects of fitness and body mass index (BMI) on all-cause and CVD mortality.[8] We found that both fitness and fatness were associated with mortality from all causes and from CVD and that fit men and women were not protected from increased risk associated with fatness.

Additional studies in other populations are needed. In an effort to broaden the reports on this topic to more diverse groups, we undertook the examination of the fitness and fatness controversy in men living in Russia (previously United Soviet Socialist Republic (USSR)). The current study examines the magnitude of the effects of cardiorespiratory fitness and BMI on mortality from all causes and from CVD

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in Russian men and contrasts those findings with those from US men obtained using the same methodologies and analytic strategies.

## Materials and methods

### The lipids research clinics (LRC) cohort

The data used in these analyses were collected as part of the Joint US–Russia LRC First Prevalence Studies and the Mortality Follow-up Studies.[9] The US sample was drawn from eight geographically diverse centers in the United States between 1972 and 1976. The Russian sample was drawn from well-defined residential areas of two major cities (Moscow and St Petersburg, previously Leningrad) between 1975 and 1977. In both the US and Russia, a two-stage procedure was used to select participants. A brief initial examination was followed by a more extensive examination. In the Russian sample, the second examination followed the first by 2–6 weeks and in the US sample, the median time between examinations was 96 days. For both cohorts participants in the second examination consisted of a 15% random sample of all visit 1 participants and 100% of those with elevated plasma lipids and those taking lipid-lowering medications. In the US cohort, the response rates for each strata was 85%, and in the Russian cohort, the response rates were 90% for each strata. It was during the second examination that cardiorespiratory fitness measures were obtained, and this examination provided the baseline measures for this study.

The Russian sample included 1989 men 40–59 y of age. Therefore, only men in this age range were included here from the US sample ($n=2354$). Unfortunately, fitness tests were done on only a subsample of the Russian women, and therefore, there were inadequate data to examine associations with fitness in Russian women. Results on associations of fitness and fatness with mortality in US women in the LRC study have been published elsewhere.[8,10] To reduce confounding from pre-existing illness[11,12] participants who died in the first year of follow-up, participants who reported a history of coronary heart disease or stroke and participants with a BMI less than 18.5 kg/m$^2$ were excluded ($n=306$ Russian and 155 American). Since heart rate response to exercise was used as an indicator of fitness, we excluded participants taking medication that may alter heart rate and participants with heart rates outside our quality control limits (resting heart rate less than 40 or greater than 120 bpm or a maximum heart rate greater than 250 bpm). We also excluded participants with a positive graded exercise test indicating possible CVD and participants with contraindications for participating in the exercise test (eg aortic stenosis, congestive heart failure, excessive blood pressure at rest, R-on-T type premature ventricular contractions, ventricular tachycardia, parasystolic focus, atrial flutter, atrial fibrillation, congenital heart disease).[13] If the duration of the graded exercise test was less than 1 min, participants were excluded since a steady state for exercise was not reached. These criteria resulted in the exclusion of an additional 311 Russian men and 201 American men. Overall, 13 Russian men and 14 US men who were missing data on height, weight or covariates used in our analyses were excluded. The final analysis sample included 3075 men: 1359 from Russia and 1716 from the US.

### Measurements

The Russian and US cohorts were studied using uniform protocols and procedures for most variables and a single Coordinating Center. Height and weight were measured with the participant wearing light clothing and no shoes. Weight was measured to the nearest 0.1 kg using a balance scale. Height was measured to the nearest 0.5 cm using a headboard and a vertical rule fixed to a wall. Fatness was assessed as BMI and calculated as weight in kilograms divided by height in meters squared. Quintiles of fatness and fitness were formed using the data from the Russian men in order to maximize the statistical power in that group.

Cardiorespiratory fitness, here called 'fitness' for the remainder of this report, was quantified as the duration of the exercise test in minutes. Participants were told to refrain from eating for 2 h prior to testing and most tests were performed in the morning. The test was conducted according to a Bruce protocol, as described in previous publications.[14–16] Seven, 3-min stages were used in which the speed and inclination were increased in a stepwise fashion as follows: Stage 1–1.7 miles per hour (MPH) and 10% inclination; Stage 2–2.5 MPH and 12% inclination; Stage 3–3.4 MPH and 14% inclination; Stage 4–4.2 MPH and 16% inclination; Stage 5–5.0 MPH and 18% inclination; Stage 6–5.5 MPH and 20% inclination; Stage 7–6.0 MPH and 22% inclination.

The electrocardiogram was monitored continuously and blood pressure was measured at the end of each stage. Heart rate was monitored continuously and was also recorded at the end of each stage, or earlier if the participant stopped during a stage. The test was terminated early if the participant was unable to continue because of chest pain, fatigue, dyspnea, or leg pain or because of abnormalities in the electrocardiogram ($\geq 1$ mm horizontal ST-segment change, major arrhythmias or conduction defects), a decrease in systolic blood pressure, technical difficulties, or if participants were unwilling to continue. Otherwise, the test was stopped when the participant attained 90% of predicted maximal heart rate (based on age and physical training[15,17]) and either maintained it for 1 min, maintained it to the end of the stage, or exceeded the target heart rate by 8 bpm, whichever occurred first.[15]

Education was categorized as: less than high school graduate, high school graduate or more than high school. Cigarette smoking was categorized as: current $>20$ cigarettes per day, current $=20$ cigarettes per day, current $<20$ cigarettes per day, former or never. Participants were questioned on the type and amount of different types of

alcoholic beverages consumed in the past 7 days and average grams of ethanol per day was calculated. Dietary intake was assessed with a 24 h recall and Keys score was calculated as described by Anderson *et al*.[18]

Physical activity was assessed with two questions and categorized as: (1) Very active: Individuals reporting strenuous exercise $\geq 3$ times per week; (2) Moderately active: Individuals reporting strenuous activity $<3$ times per week; (3) Inactive: Individuals reporting no strenuous exercise.[19]

### Vital status follow-up

Standardized procedures were used to collect mortality follow-up information on the Russian and US cohorts. Deaths were obtained by annual follow-up contacts with the cohort (predominantly by phone) up to the end of 1987. At the end of 1987, vital status was known on 99.4% of the Russian cohort and 99.6% of the US cohort. Subsequent to 1987 annual follow-up contacts were continued for the Russian cohort, but the US cohort was followed by searching the National Death Index (1988–1991) and the Epidemiology Research Index (1992–1995). Cause of death was ascertained by nosologist's codings (International Classification of Deaths) of the death certificates for the entire follow-up in both countries. We used ICD-9 codes 390–459 to identify CVD deaths. For both cohorts, vital status follow-up through 1995 was used here.

### Statistical analysis

Mortality rates were calculated averaging across lipid strata using the inverse of the sampling probability as the weight. Associations between BMI and fitness and mortality were examined using stratified Cox proportional hazards models, with the sampling strata (hyperlipidemics and normolipidemics) as the stratifying variable. These analytic techniques permit inferences to be made to the samples screened at visit 1. The Statistical Analysis System[20] was used to conduct analyses.

## Results

The mean BMI and fitness measures were similar in Russian and American men. Among Russian men, 36% were normal weight (BMI 18.5–24.9 kg/m$^2$), 51% were overweight (BMI 25.0–29.9 kg/m$^2$) and 13% were obese (BMI $\geq 30$ kg/m$^2$). Among US men, 31% were normal weight, 54% were overweight and 15% were obese. The mean (s.d.) time on the treadmill was 9.8 (1.9) min over all Russian men and 9.4 (2.2) min in US men. Metabolic equivalent (MET) values were extrapolated from published exercise intensities,[13,21] and yielded corresponding values of 11.1 METS (stage 4) for Russian men and 10.6 METS (stage 4) for US men. These values represent the capacity required to walk on the treadmill at the corresponding speed and grade. Most participants stopped the exercise test beyond 90% of predicted maximal heart rate. In Russian men, the median was 96.9% (interquartile range 93.0–99.6%) and 97.7% in US men (interquartile range 94.3–100%).

Fitness tended to decline as BMI increased, however, the unadjusted correlation between BMI and fitness was not very high: $r=-0.12$ in Russian men, $-0.10$ in US men. Among Russian men, 9% who were obese were in the most-fit quintile, while 19% were in the least-fit quintile. Among normal weight Russian men, 42% were in the most-fit quintile, while 34% were in the least fit. For US men, 10% who were obese were in the most-fit quintile, while 20% were in the least-fit quintile. Among normal weight US men, 35% were in the most-fit quintile, while 28% were in the least fit. As shown in Table 1, Russian and US men in the 5th quintile of BMI tended to have lower scores on the graded exercise test compared to men with lower BMI values, and men in the first quintile of fitness tended to be heavier than more fit men.

Overall, dietary Keys scores were similar in the two groups of men (US: 58.5 and Russian: 58.6), while alcohol consumption was higher in US than in Russian men (15.1 and 13.5 g, respectively). The percentage of men in 5th quintile of BMI that had less than a high school education was larger in Russian men (34%) than in American men (18%). Similarly, the proportion of men in the first quintile of fitness who had less than a high school education was also higher among the Russian men (39%) than the American men (11%). Overall, smoking was more prevalent among Russian men (56%) than in US men (35%). The percentage of never smokers was higher in the 5th quintile of BMI than in the other quintiles, and higher in fitness quintiles 2–5 than in the least-fit quintile. Overall, 68% of Russian men and 66% of US men were in the lowest physical activity category.

Confounding by pre-existing illness was tested by examining coefficients for BMI and fitness after excluding participants who died in the first year *vs* the first 4 y of follow-up.[12] The hazard ratios were very similar in both sets of analyses and varied by less than 1%. Therefore, deaths in years 2–4 of follow-up were not excluded.

We examined possible confounding of BMI by cigarette smoking by examining the BMI–mortality association within smokers and nonsmokers in the Russian and US men separately. We used the full covariate adjusted model, and included indicators for former *vs* never smoking in the analyses of nonsmokers and indicators of smoking dose ($<20$, $=20$, $>20$ cigarettes per day) in the analyses of the smokers. In analyses that examined BMI in quintiles, there was no evidence that the hazard ratio associated with the lowest quintile of BMI (18.6–22.8 kg/m$^2$), compared to the second quintile (22.9–24.8 kg/m$^2$), was elevated in smokers compared to nonsmokers, and there was no evidence of an accentuated J- or U-shape in the smokers compared to the nonsmokers. There was also no indication that the association of elevated BMI with all-cause or CVD mortality was systematically attenuated in smokers compared to nonsmokers in the highest *vs* the lowest quintiles of BMI analysis. In addition, two-way interactions of smoking

**Table 1** Description of analysis sample by quintiles of BMI and fitness from the Lipids Research Clinics Prevalence Study

| | *Russian men (n = 1359)* | | | | *United States men (n = 1716)* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Mean ± s.d. or percentage* | | | | *Mean ± s.d. or percentage* | | | |
| | *BMI quintiles 1–4* | *BMI 5th quintile* | *Fitness 1st quintile* | *Fitness quintiles 2–5* | *BMI quintiles 1–4* | *BMI 5th quintile* | *Fitness 1st quintile* | *Fitness quintiles 2–5* |
| Age (y) | 48.5 ± 5.1 | 49.0 ± 5.2 | 50.1 ± 5.4 | 48.2 ± 5.0 | 48.4 ± 6.3 | 48.0 ± 6.2 | 50.0 ± 6.4 | 47.5 ± 6.0 |
| BMI (kg/m$^2$) | 24.9 ± 2.3 | 30.6 ± 1.8 | 26.8 ± 3.7 | 26.1 ± 3.1 | 25.3 ± 2.0 | 31.2 ± 2.6 | 27.4 ± 3.8 | 26.6 ± 3.2 |
| Graded Exercise Test (min) | 9.9 ± 1.9 | 9.3 ± 1.8 | 7.2 ± 1.3 | 10.5 ± 1.3 | 9.5 ± 2.2 | 9.2 ± 2.1 | 7.1 ± 1.4 | 10.6 ± 1.4 |
| Alcohol (g/day) | 13.3 ± 21.1 | 14.0 ± 20.5 | 13.1 ± 22.1 | 13.6 ± 20.6 | 15.0 ± 19.8 | 15.4 ± 22.1 | 17.4 ± 23.0 | 14.0 ± 19.0 |
| Smoking (cigarettes/day) | 11.1 ± 11.0 | 7.5 ± 10.4 | 11.3 ± 11.3 | 9.9 ± 10.8 | 9.7 ± 15.6 | 9.0 ± 17.1 | 10.6 ± 16.6 | 9.0 ± 15.7 |
| Keys Score | 58.4 ± 16.0 | 58.5 ± 16.4 | 58.6 ± 15.5 | 58.4 ± 16.3 | 51.3 ± 15.2 | 53.6 ± 15.9 | 51.8 ± 16.3 | 52.0 ± 15.0 |
| Education (%) | | | | | | | | |
| Less than high school | 34 | 34 | 39 | 33 | 12 | 18 | 11 | 15 |
| High school | 26 | 25 | 23 | 26 | 34 | 36 | 32 | 35 |
| Greater than high school | 40 | 41 | 39 | 41 | 54 | 48 | 56 | 50 |
| Smoking (%) | | | | | | | | |
| Never smoked | 20 | 22 | 16 | 21 | 26 | 29 | 23 | 28 |
| Quit smoking | 21 | 34 | 24 | 24 | 38 | 40 | 39 | 38 |
| Current smoker | | | | | | | | |
| Less than 20/day | 22 | 22 | 21 | 22 | 8 | 8 | 8 | 8 |
| 20/day | 23 | 13 | 23 | 20 | 10 | 7 | 10 | 9 |
| Greater than 20/day | 14 | 10 | 16 | 12 | 19 | 16 | 21 | 17 |
| Physical activity (%) | | | | | | | | |
| Very active | 31 | 25 | 21 | 32 | 27 | 26 | 17 | 32 |
| Moderate active | 2 | 1 | 2 | 2 | 7 | 7 | 5 | 7 |
| Not active | 67 | 73 | 77 | 66 | 66 | 67 | 79 | 61 |

with either BMI quintiles or with fitness quintiles were not significant.

Overall, the age-adjusted rates for mortality from both all causes and CVD mortality were higher in the Russian men (13.5 and 6.5 per 100 000 person-years) than in the US men (9.8 and 3.8 per 100 000 person-years). The number of deaths and the age-adjusted death rates for each quintile of BMI and fitness are shown in Table 2. In Russian men, the highest all-cause mortality rate was seen in the lowest quintile of BMI and the rate tended to decline as BMI increased. This differed from what was seen in US men in whom the highest all-cause death rate was in the quintile with the highest BMI. For CVD mortality there was no pattern among Russian men, but in US men the death rate tended to increase with increasing BMI quintiles. For fitness, the age-adjusted death rate was consistently highest in the least-fit quintile for both all-cause and CVD mortality for both Russian and the US men.

Table 3 shows associations between BMI and all-cause and CVD mortality, with and without adjustment for fitness (in the continuous form). The hazard ratios showed no statistically significant differences among the BMI quintiles in either Russian or American men. The highest BMI quintile tended to be associated with the highest relative risk in all comparisons in the US men. For fitness, the hazard ratio was elevated for the least-fit quintile compared to the most-fit quintile, although the *P*-value for this difference was not less than 0.05 for CVD mortality in the US men. The addition of BMI to the models examining fitness, and the addition of fitness to the models examining BMI changed the hazard ratios only slightly.

Figure 1 shows the hazard ratios for participants categorized as fit-not fat (the reference), fit-fat, unfit-fat, and unfit-not fat. For this analysis, both fitness and fatness were categorized using the highest risk quintile (Quintile 5 for BMI, Quintile 1 for fitness) *vs* all other quintiles combined. In Russian men, the hazard ratios for mortality from all causes (0.87, 95% CI: 0.55, 1.37) and from CVD (0.94, 95% CI: 0.49, 1.81) were not elevated in the fit-fat group, and in fact the point estimates were less than one. The hazard ratios were increased for both outcomes in both the unfit-not fat group and the unfit-fat group. Although the hazard ratio for CVD mortality appeared greater in the unfit-fat men (3.05, 95% CI: 1.74, 5.34) than in the unfit-not fat men (1.85, 95% CI: 1.09, 3.15) the confidence intervals overlapped. In US men, for all-cause mortality, the hazard ratio was increased above the reference for all the groups. For CVD mortality, the hazard ratios were also increased, but the difference was not statistically significant in the fit-fat group (1.32, 95% CI: 0.85, 2.06). Two-way interactions between fitness and fatness were tested for all-cause and CVD mortality in the Russian and the US men and none were statistically significant.

## Discussion

In the LRC cohort, fitness was associated with all-cause and CVD mortality in both the US and Russian men. BMI was not

**Table 2** All-cause and CVD death rates by quintiles of BMI and fitness for LRC Russian and US men[a]

| | *BMI*[b] | | *Fitness*[c] | |
|---|---|---|---|---|
| | *Number of deaths* | *Age-adjusted death rate (per 100 000 person-years)* | *Number of deaths* | *Age-adjusted death rate (per 100 000 person-years)* |
| *Russian men* | | | | |
| *All-cause mortality* | | | | |
| Quintile 1 | 38 | 18.2 | 77 | 19.9 |
| Quintile 2 | 41 | 13.2 | 36 | 9.2 |
| Quintile 3 | 45 | 13.7 | 32 | 9.8 |
| Quintile 4 | 36 | 9.7 | 39 | 13.3 |
| Quintile 5 | 51 | 11.9 | 27 | 8.8 |
| *CVD mortality* | | | | |
| Quintile 1 | 10 | 5.0 | 40 | 9.8 |
| Quintile 2 | 15 | 4.6 | 18 | 4.7 |
| Quintile 3 | 22 | 7.0 | 10 | 2.8 |
| Quintile 4 | 19 | 5.1 | 18 | 6.2 |
| Quintile 5 | 32 | 7.3 | 12 | 3.8 |
| *US men* | | | | |
| *All-cause mortality* | | | | |
| Quintile 1 | 41 | 12.0 | 193 | 14.0 |
| Quintile 2 | 79 | 10.7 | 80 | 11.5 |
| Quintile 3 | 100 | 10.9 | 70 | 12.9 |
| Quintile 4 | 97 | 11.1 | 72 | 9.0 |
| Quintile 5 | 143 | 14.4 | 45 | 10.0 |
| *CVD mortality* | | | | |
| Quintile 1 | 16 | 4.9 | 80 | 5.9 |
| Quintile 2 | 26 | 3.4 | 29 | 4.2 |
| Quintile 3 | 39 | 4.3 | 27 | 5.1 |
| Quintile 4 | 43 | 4.9 | 23 | 3.0 |
| Quintile 5 | 54 | 5.6 | 19 | 4.4 |

[a]Adjusted for lipid strata and age adjusted using 5-y age strata and the distribution of age in visit 1. [b]Q1: 18.6–22.8, Q2: 22.9–24.8, Q3: 24.9–26.5, Q4: 26.6–28.5, Q5: 28.6–37.4. [c]Q1: 1.5–8.8, Q2: 8.9–9.5, Q3: 9.6–10.2, Q4: 10.3–11.6, Q5: 11.7–18.0.

associated with either outcome in the Russian men. In US men, BMI tended to be a significant predictor of both outcomes but was statistically significant only for all-cause mortality in the final models shown in Figure 1. We have previously reported the association between BMI and CVD and all-cause mortality in 30–74 y-old US men in this cohort.[8] In the current study, the age range of the men included in the study sample was restricted to 40–59 y and the mortality follow-up was truncated by 3 y to match the data available in the Russian men. In addition, the quintiles were formed using the distributions of BMI and fitness in the Russian cohort, and so cut points varied slightly between the studies. All these changes reduced the statistical power available in the US men in the current study compared to the previous study. In both analyses of US men, there were no statistically significant differences in all-cause mortality in BMI quintiles 1–4 (separately) compared to the first BMI quintile, however, in the earlier analysis there was a statistically significant increase in CVD mortality observed, even after controlling for fitness level (hazard ratio for fifth compared to first BMI quintile was 1.56, 95% CI: 1.01, 2.41). In the models that compared the 5th quintile of BMI to quintiles 1–4 (combined), findings were very similar between the two studies and the largest discrepancy noted between the hazard ratios in the two studies was 0.15.

In an earlier report on the Russian men from the LRC study Shestov *et al*[22] found a significant quadratic association between Quetelet Index ($kg/cm^2 \times 1000$) and all-cause and CVD mortality. Their analyses of crude mortality rates showed a sharp elevation in all-cause mortality for men in the lowest quintile of Quetelet Index (23 deaths per 1000 person-years). The lowest mortality rate was observed in the 3rd quintile of Quetelet index (9 deaths per 1000 person-years), and the death rate was somewhat higher in the 5th quintile (10.5 deaths per 1000 person-years). Differences between quintiles of Quetelet Index were smaller for CVD mortality, but followed the same general pattern. This study by Shestov *et al* had only 7 y of follow-up, whereas the follow-up in the current study was as long as 23 y with a mean of 17.6 y. In our analyses an elevated death rate was not observed in the lowest quintile of BMI, and this difference from the previous work may have been due to the exclusions and covariate adjustments used to avoid sources of confounding and/or to the longer follow-up period.

We know of no other studies that have examined associations between fitness and mortality in Russian men, however, two previous papers have examined data obtained during the treadmill test from the Russian men in the LRC study. The first examined blood pressure and heart rate response during the exercise test.[23] The investigators found that Russian men had higher resting systolic blood pressure than US men, but lower blood pressure during exercise. Russian men had significantly lower heart rate at rest and during exercise compared to US men. In the second report,[24] resting heart rate was examined as a predictor of cardiovascular and total mortality. Age- and clinic-adjusted hazard ratios examining a resting heart rate increment of 10 bpm were similar among the Russian and US men for both mortality from all causes (Russian hazard ratio = 1.35, 95% CI: 1.22, 1.55; US hazard ratio = 1.40, 95% CI: 1.23, 1.60). and CVD mortality (Russian hazard ratio = 1.32, 95% CI: 1.13, 1.53; US hazard ratio = 1.42, 95% CI: 1.18, 1.70).

We found that the time on the treadmill was a significant predictor of all-cause and CVD mortality. The results were similar among the Russian and US men, although the hazard ratios comparing the first to the 5th (reference) quintile tended to be larger in the Russian men (over 2 for all-cause and CVD mortality) than in the US men (approximately 1.4–1.5 for the same estimates). Our previous study of US men in a broader range of ages[8] gave similar results with hazard ratios for the first *vs* the 5th quintile of fitness in the range of approximately 1.5–1.6.

In the LRC cohort, the age-adjusted death rate from all causes was 37% higher in Russian men than in US men,

**Table 3** Adjusted hazard ratios[a] (95% confidence intervals—CI) by quintiles of BMI and fitness for LRC Russian and US men

| | *BMI*[b] | | | | *Fitness*[c] | | | |
|---|---|---|---|---|---|---|---|---|
| | *Hazard ratio* | *95% CI* | *Hazard ratio adjusted for fitness* | *95% CI* | *Hazard ratio* | *95% CI* | *Hazard ratio adjusted for BMI* | *95% CI* |
| *Russian men* | | | | | | | | |
| *All-cause mortality* | | | | | | | | |
| Quintile 1 | 1.00 | | 1.00 | | 2.10 | 1.32–3.33 | 2.13 | 1.34–3.38 |
| Quintile 2 | 0.87 | 0.55–1.39 | 0.90 | 0.56–1.44 | 1.05 | 0.62–1.77 | 1.07 | 0.63–1.81 |
| Quintile 3 | 1.16 | 0.72–1.86 | 1.19 | 0.74–1.92 | 1.11 | 0.65–1.88 | 1.10 | 0.65–1.87 |
| Quintile 4 | 0.84 | 0.51–1.38 | 0.88 | 0.53–1.44 | 1.42 | 0.84–2.38 | 1.41 | 0.84–2.38 |
| Quintile 5 | 0.92 | 0.57–1.47 | 0.88 | 0.55–1.41 | 1.00 | | 1.00 | |
| *CVD mortality* | | | | | | | | |
| Quintile 1 | 1.00 | | 1.00 | | 2.23 | 1.16–4.29 | 2.17 | 1.12–4.18 |
| Quintile 2 | 1.04 | 0.45–2.43 | 1.07 | 0.46–2.50 | 1.01 | 0.48–2.14 | 0.98 | 0.46–2.07 |
| Quintile 3 | 1.83 | 0.82–4.08 | 1.88 | 0.84–4.22 | 0.65 | 0.27–1.54 | 0.65 | 0.27–1.54 |
| Quintile 4 | 1.33 | 0.58–3.03 | 1.40 | 0.61–3.21 | 1.25 | 0.58–2.68 | 1.25 | 0.58–2.68 |
| Quintile 5 | 1.82 | 0.84–3.95 | 1.74 | 0.80–3.79 | 1.00 | | 1.00 | |
| *US men* | | | | | | | | |
| *All-cause mortality* | | | | | | | | |
| Quintile 1 | 1.00 | | 1.00 | | 1.54 | 1.10–2.14 | 1.51 | 1.08–2.11 |
| Quintile 2 | 0.87 | 0.60–1.28 | 0.86 | 0.59–1.25 | 1.28 | 0.88–1.84 | 1.27 | 0.88–1.83 |
| Quintile 3 | 0.88 | 0.61–1.27 | 0.90 | 0.62–1.30 | 1.33 | 0.91–1.95 | 1.34 | 0.92–1.95 |
| Quintile 4 | 0.90 | 0.62–1.31 | 0.88 | 0.61–1.28 | 1 | 0.69–1.46 | 1 | 0.69–1.45 |
| Quintile 5 | 1.15 | 0.80–1.65 | 1.11 | 0.77–1.59 | 1.00 | | 1.00 | |
| *CVD mortality* | | | | | | | | |
| Quintile 1 | 1.00 | | 1.00 | | 1.45 | 0.86–2.43 | 1.43 | 0.85–2.40 |
| Quintile 2 | 0.72 | 0.38–1.34 | 0.71 | 0.38–1.32 | 1.07 | 0.60–1.92 | 1.06 | 0.59–1.91 |
| Quintile 3 | 0.87 | 0.48–1.56 | 0.90 | 0.50–1.63 | 1.20 | 0.66–2.18 | 1.20 | 0.66–2.19 |
| Quintile 4 | 0.98 | 0.55–1.76 | 0.96 | 0.53–1.72 | 0.74 | 0.40–1.36 | 0.74 | 0.40–1.35 |
| Quintile 5 | 1.07 | 0.60-1.91 | 1.02 | 0.57–1.82 | 1.00 | | 1.00 | |

[a]Adjusted for age, smoking, education, alcohol, and Keys score. [b]Q1: 18.6–22.8, Q2: 22.9–24.8, Q3: 24.9–26.5, Q4: 26.6–28.5, Q5: 28.6–37.4. [c]Q1: 1.5–8.8, Q2: 8.9–9.5, Q3: 9.6–10.2, Q4: 10.3–11.6, Q5: 11.7–18.0.

whereas the CVD death rate was 70% higher. During the years of this study of Russian men (1975–1995) there were important social, political and economic changes in Russia that dramatically impacted the death rate. After World War II life expectancy in Russia rose rapidly, and for the first time in recorded history became similar to that of Western countries. In 1965, male life expectancy was 64.3 y in Russia compared to 67.5 in France and 66.8 in the United States.[25] As summarized by Notzon *et al*,[26] after that time life expectancy went through two decades of decline in Russia, while it increased steadily in the United States. Between 1985 and 1987 life expectancy abruptly increased in Russia. This increase has been attributed to the sudden drop in per capita alcohol consumption brought about by Gorbachev's anti-alcohol campaign, and may also have been stimulated by the period of 'perestroika' that introduced the notion of social democratization. However, between 1990 and 1994 life expectancy in Russia again dropped and the age-adjusted mortality rates rose by approximately 33%. In 1994, life expectancy for Russian men was 57.7 y compared to 72.4 y in US men. The most important contributors to this decline in life expectancy were cardiovascular diseases (36%) and injuries (29%).[26]

Given the differences in the patterns of mortality in the two nations over the study period it is remarkable that the associations with fitness were so similar between the two groups of men, while the associations with BMI were different. One possible explanation for this difference is that the association between BMI and mortality was attenuated by confounding, while the association between fitness and mortality was not. We can only speculate on this point.

One potential confounding factor is alcohol intake. Self-report of alcohol intake is known to be susceptible to subject response bias related to social desirability. The Russian data reported here were collected between 1975 and 1977, which was 5–10 y before aggressive public health measures to limit alcohol intake were instituted. Therefore, it does not seem very likely that this group of Russian men would be strongly motivated to under-report alcohol consumption. Further, it seems unlikely that reported alcohol consumption would be differentially biased by weight status, but not by fitness status. Nevertheless, it is troublesome that reported alcohol intake was slightly lower in the Russian men than in the US men in this study, as other studies indicate the opposite.[27]

Of course, many factors other than alcohol differed between the Russian and the US men in this study and

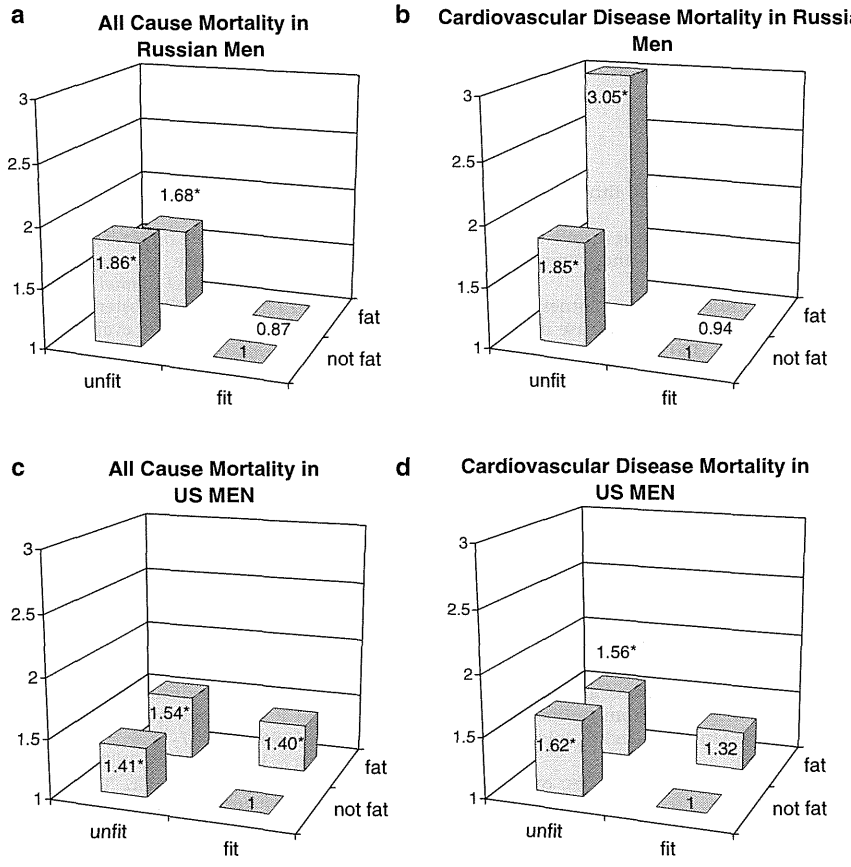


**Figure 1** Relative hazard in LRC participants categorized by fitness level (quintile 1 *vs* 2–5) and BMI (quintiles 1–4 *vs* 5) adjusted for age, education, smoking, alcohol, and Keys score. * = $P<0.05$. Hazard ratios were calculated using the fit-not fat group as the reference. Estimates and 95% confidence intervals (CI) for the fit-fat, the unfit-not fat and the unfit-fat were: all-cause mortality in Russian men, 0.87 (0.55, 1.37), 1.86 (1.31, 2.62), 1.68 (1.06, 2.68); CVD mortality in Russian men, 0.94 (0.49, 1.81), 1.85 (1.09, 3.15), 3.05 (1.74, 5.34); all-cause mortality in US men, 1.40 (1.07, 1.83), 1.41 (1.12, 1.77), 1.54 (1.24, 2.06); CVD mortality in US men, 1.32 (0.85, 2.06), 1.62 (1.01, 2.58), 1.56 (1.08, 2.24).

could have influenced the measured effect of BMI on mortality. Some other potential factors are tobacco use, diet, stress and depression, health care availability and pollution. Although we attempted to control for the effects of tobacco use and diet in our analysis, residual confounding could still remain for these factors. We were unable to control for the other factors.

This study has several strengths and limitations. As in our previous study[8] we chose to form joint categories of fitness and fatness drawing the cut point at the boundary of the highest risk quintile for both BMI and fitness. This method of categorization is arbitrary, but it has the advantage of providing a cut point for the two different measures that is equivalent in at least one aspect, that is, as marker of the 20% at highest risk among the population studied. Other methods of defining these groups could have been used. It should also be noted that BMI is an imperfect measure of adiposity and a more precise measure of body composition could have given different results.

The cohorts studied were not nationally representative samples of either US men or Russian men, but they were drawn from well-defined groups. It is a weakness that the comparability of the nosologists' diagnoses of primary cause of death in the US *vs* in Russia is not known. Because of this, comparisons of cause-specific deaths must be made with caution. It is a strength of the study that the cohorts drawn from such different locations were studied using the same procedures and a single coordinating center.

This study of two populations of men living in very different environments was able to compare the effects of fitness and fatness on mortality. As has been shown before, both fitness and fatness were associated with all-cause and CVD mortality in American men. However in the Russian men, fitness but not fatness, was associated with both types of mortality. This study gives some indication that the effects of fitness on mortality may be more robust across populations than are the effects of fatness.

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## References

1 Barlow C, Kohl H, Gibbons L, Blair S. Physical fitness, mortality and obesity. *Int J Obes* 1995; **19**: S41–S44.
2 Blair S, Kohl H, Paffenbarger R. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989; **262**: 2395–2401.
3 Lee C, Blair S, Jackson A. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 1999; **69**: 373–380.
4 Farrell SW, Kampert JB, Kohl HW, Barlow CE, Macera CA, Paffenbarger RS, Gibbons LW, Blair SN. Influences of cardiorespiratory fitness levels and other predictors on cardiovascular disease mortality in men. *Med Sci Sports Exerc* 1998; **30**: 899–905.
5 Lee C, Jackson A, Blair S. US weight guidelines: Is it also important to consider cardiorespiratory fitness? *Int J Obes Relat Metab Disord* 1998; **22** (Suppl 2): S2–S7.
6 Wei M, Gibbons L, Mitchell T, JB K, Lee C, Blair S. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Int Med* 1999; **130**: 89–96.
7 Farrell S, Braun L, Barlow C, Cheng Y, Blair S. The relation of body mass index, cardiorespiratory fitness, and all-cause mortality in women. *Obes Res* 2002; **10**: 417–423.
8 Stevens J, Cai J, Evenson K, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the Lipid Research Clinics Study. *Am J Epidemiol* 2002; **156**: 832–841.
9 Levy R, Klimov A, Williams O. Epidemiology studies: overview. *Atherosclerosis Rev* 1988; **17**: 93–102.
10 Evenson KR, Stevens J, Cai J, Thomas R, Thomas O. The effect of cardiorespiratory fitness and obesity on cancer mortality in women and men: The Lipids Research Clinics Study. *Med Sci Sports Exerc* 2003; **35**: 270–277.
11 Manson J, Stampfer M, Hennekens C, Willett W. Body weight and longevity. *JAMA* 1987; **257**: 353–358.
12 Stevens J, Juhaeri, Cai J. Changes in body mass index prior to baseline among participants who are ill or who die during the early years of follow up. *Am J Epidemiol* 2001; **153**: 946–953.
13 American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. Lippincott, Williams & Wilkins: Philadelphia, PA; 2000.
14 Sheffield L, Roitman D. Stress testing methodology. *Prog Cardiovasc Dis* 1976; **19**: 33–49.
15 Sheffield LT, Haskell W, Heiss G, Kioschos M, Leon A, Roitman D, Schrott H. Safety of exercise testing volunteer subjects: the Lipid Research Clinics' Prevalence Study experience. *J Cardiac Rehab* 1982; **2**: 395–400.
16 Ekelund L, Haskell W, Johnson J, Whaley F, Criqui M, Sheps D. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. *N Engl J Med* 1988; **319**: 1379–1384.
17 Bruce R, Fisher L, Cooper E, Al E. Separation of effects of cardiovascular disease and age on ventricular function with maximal exercise. *Am J Cardiol* 1974; **34**: 757–763.
18 Anderson JT, Jacobs DR, Foster N, Hall Y, Moss D, Mojonnier L, Blackburn H. Scoring for evaluating dietary pattern effect on serum cholesterol. *Prev Med* 1979; **8**: 525–537.
19 Pereira MA, FitzGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc* 1997; **29**: S15–S18.
20 SAS Institute I. *SAS/STAT User's Guide*. SAS Institute Inc.: Cary, NC; 1988.
21 Bruce R. Exercise testing for ventricular function. *N Engl J Med* 1977; **296**: 671–675.
22 Shestov D, Deev A, Zhukovsky G, Thorn M, Davis C, Klimov A. Coronary heart disease risk factors and mortality in the USSR lipid research clinics follow-up study. *Atherosclerosis Rev* 1988; **17**: 261–275.
23 Shalnova S, Shestov DB, Ekelund L, Abernathy JR, Plavinskaya S, Thomas RP, Williams DH, Deev A, Davis CE. Blood pressure and heart rate response during exercise in men and women in the USA and Russia lipid research clinics prevalence study. *Atherosclerosis* 1996; **122**: 47–57.
24 Shalnova S, Plavinskaya S, Williams D, Deev A, Shestov D, Irving S, Zhukovsky G, Davis CE. The association of heart rate and mortality in Russian and US men aged 40–59. *Cardiovasc Risk Factors* 1997; **7**: 36–42.
25 Shkolnikov V, Meslé F, Vallin J. Recent trends in life expectancy and causes of death in Russia, 1970–1993. In: Bobadilla J, Costello C, Mitchell F (eds). *Premature Death in the New Independent States*. National Academy Press: Washington, DC; 1997. pp 34–65.
26 Notzon F, Komarov Y, Ermakov S, Sempos C, Marks J, Sempos E. Causes of declining life expectancy in Russia. *JAMA* 1998; **279**: 793–800.
27 Treml V. Soviet and Russian statistics on alcohol consumption and abuse. In: Bobadilla J, Costello C, Mitchell F (eds). *Premature Death in the New Independent States*. National Academy Press: Washington, DC; 1997. pp 220–228.

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|---|---|---|---|---|---|---|---|
| | 対象 | 一般健常者 | 空白 | | ( ) | | コホート研究 |
| | 性別 | 男性 | ( ) | | ( ) | | ( ) |
| | 年齢 | 40-59歳 | | | ( ) | | 前向き研究 |
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| 調査の方法 | | 実測 | ( ) | | | | |
| アウトカム | 予 防 | な し | な し | な し | な し | ( 死亡 ) | ( ) |
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|---|---|
| 図 表 | |
| 図表掲載箇所 | |
| 概 要<br>(800字まで) | 目的:ロシア人男性の死亡率おいて、体力と肥満の影響の相対的な大きさを調査し、米国の男性と比較すること。デザイン:プロスペクティブクロースドコホートスタディ。対象者:Lipids Research Clinics Studyに登録され、ベースライン時において40-59歳の1359名のロシア人男性および1716名の米国男性。測定項目:体力はトレッドミルテストを用いて評価され、肥痩度は身長と体重から算出されたBMIを評価した。リスク比は、年齢、教育、喫煙、アルコール摂取量、および食事の主要因子を共変量として含んだ比例ハザードモデルを用いて計算した。全死亡原因と心血管疾患(CVD)死亡率は、1995まで観察した。結果:ロシア人男性では、体力は全死亡原因とCVD死亡率で関連性がみられたが、肥満とは関連しなかった。全死亡原因において、肥満でない高体力者と比べて、補正されたリスク比は肥満で高体力者で0.87[0.55、1.37](95%信頼区間)、肥満でない低体力者で1.86[1.31、2.62](95%信頼区間)、肥満で低体力者で1.68[1.06、2.68](95%信頼区間)であった。米国男性の中では、同じリスク比は、それぞれ1.41[1.12、1.77](95%信頼区間)、1.54[1.24、2.06](95%信頼区間)、および1.40[1.07、1.83](95%信頼区間)であった。全死亡原因もしくはCVD死亡率において、いずれのグループの男性にも体力と肥満との間には統計的に有意な交互作用はなかった。結論:人種(種族)間の違いを問わず、死亡率における体力の影響は、肥満の影響よりも強健であるかもしれない。 |
| 結 論<br>(200字まで) | 8.8メッツ未満の心肺体力だと、ロシア人では肥満度に関わらず総死亡も循環器病死亡もリスクが増大する。アメリカ人では非肥満者のみリスクが増大する。 |
| エキスパートによるコメント<br>(200字まで) | 肥満でも体力があれば生活習慣病リスクが高くないという研究。 |

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# Prospective study of cardiorespiratory fitness and depressive symptoms in women and men

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ABSTRACT

Most studies of the relationship between cardiorespiratory fitness (CRF) and depression have been limited to cross-sectional designs. The objective of this study was to follow individuals over time to examine whether those with higher levels of CRF have lower risk of developing depressive symptoms. Participants were 11,258 men and 3085 women enrolled in the Aerobics Center Longitudinal Study in Dallas, TX. All participants completed a maximal treadmill exercise test at baseline (1970–1995) and a follow-up health survey in 1990 and/or 1995. Individuals with a history of a mental disorder, cardiovascular disease, or cancer were excluded. CRF was quantified by exercise test duration, and categorized into age and sex-stratified groups as low (lowest 20%), moderate (middle 40%), or high (upper 40%). Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). Those who scored 16 or more on the CES-D were considered to have depressive symptoms. After an average of 12 years of follow-up, 282 women and 740 men reported depressive symptoms. After adjusting for age, baseline examination year, and survey response year, the odds of reporting depressive symptoms were 31% lower for men with moderate CRF (odds ratio, OR 0.69; 95% confidence interval, CI 0.56–0.85) and 51% lower for men with high CRF (OR 0.49, CI 0.39–0.60), compared to men with low CRF. Corresponding ORs for women were 0.56 (CI 0.40–0.80) and 0.46 (CI 0.32–0.65). Higher CRF is associated with lower risk of incident depressive symptoms independent of other clinical risk predictors.



## 1. Introduction

In any given year, depressive disorders affect about 18.8 million Americans, 9.5% of all adults (NIMH, 2006). The costs associated with depression for the year 2000 have been estimated at $83.1 billion (Greenberg et al., 2003). Depressive symptoms are associated with greater morbidity and mortality, less ability to function independently, and lower occupational performance (Penninx et al., 2001; Kouzis et al., 1995; Druss et al., 2000; Krishnan et al., 2002). There is also evidence suggesting that depression may increase the risks of developing Alzheimer's disease and cognitive decline (Jorm, 2000; Green et al., 2003).

Many population-based studies have reported that physical activity may reduce the risk of developing depression (Farmer et al., 1988; Camacho et al., 1991; Paffenbarger et al., 1994; Kritz-Silverstein et al., 2001; Strawbridge et al., 2002; Wiles et al., 2007; Thirlaway and Benton, 1992; Galper et al., 2006; Tolmunen et al., 2006). Meta-analyses based on cross-sectional studies, longitudinal studies, and randomized clinical trials appear to confirm this association (Lawlor and Hopker, 2001; Dunn et al., 2001; Stathopoulou et al., 2006; Blumenthal et al., 1999). However, some studies have not found this effect (Lennox et al., 1990; Cooper-Patrick et al., 1997; Weyerer, 1992). The inconsistent findings of previous research may be due to: cross-sectional analyses or experimental designs with short term follow-up; selection biases associated with age, gender, or other non-representative sampling; nonstandardized measurement of depression; and the variety of ways in which physical activity has been measured, most commonly with self-reports (Hopko et al., 2008).

For the measure of depressive symptoms, we employed the validated and widely-used Center for Epidemiologic Studies Depres-

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sion Scale (CES-D). Although the CES-D cannot diagnose depression, it is not diagnostic, the CES-D is a valid and reliable measure of depressive symptoms among adults in the general population (Beekman et al., 1997). We sought to overcome many of the limitations of previous research in the current study by examining the prospective relationship between cardiorespiratory fitness (CRF) and depressive symptoms. CRF is an objective and reproducible physiological measure that reflects functional influences of physical activity habits, genetics, and disease status. CRF has been found to be inversely associated with the risks of developing fatal and nonfatal chronic diseases (Bouchard et al., 2006; Blair et al., 1989; Blair et al., 1996; Sui et al., 2007). Less research has examined associations between CRF and emotional well being. To our knowledge, only three previous studies have investigated the association between symptoms of depression and CRF (Tolmunen et al., 2006; Galper et al., 2006; Thirlaway and Benton, 1992). One focused on middle-aged men, reporting that those with low CRF (measured by $VO_{2max}$, maximal oxygen uptake) were more likely to have depressive symptoms (Tolmunen et al., 2006). The others included both women and men (Thirlaway and Benton, 1992; Galper et al., 2006). Thirlaway and Benton (1992) studied a group of relatively young subjects, the majority between ages 30 and 40, finding an inverse association between CRF and depressive symptoms. This result was found only for those who were physically inactive, however, not for those who were at least moderately active. More recently, in the Aerobics Center Longitudinal Study (ACLS), (Galper et al. (2006) also reported that CRF was inversely associated with depressive symptoms. All of these studies were limited by their cross-sectional designs. The present study will expand the earlier report from the ACLS, by examining the longitudinal association between CRF and depressive symptoms.

## 2. Methods

### 2.1. Study population

The ACLS is a prospective epidemiological study investigating health outcomes associated with physical activity and CRF at the Cooper Clinic, Dallas, TX (Blair et al., 1989; Blair et al., 1996; Sui et al., 2007). All patients had a baseline health examination. All patients included in this study had normal resting electrocardiograms (ECGs), and were able to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate (defined as 220 minus age) during 1970–1995. The mean (SD) percentage of age-predicted maximal heart rate achieved during exercise was 101.2 (6.0) in women, and 102.5 (7.0) in men, thus indicating maximal or near maximal exertion. Those who reported having previously been diagnosed with a mental disorder – such as depression, anxiety, thoughts of suicide, nervous breakdown, difficulty sleeping, nervous disorder, or psychiatric counseling – were excluded from the analysis. We also excluded individuals with a history of myocardial infarction, stroke, or cancer, because these diseases might be related to depression and/or fitness. The current analysis included 14,343 individuals (aged 20–81 years) who met the above criteria and responded to at least one mail-back health survey in 1990 and/or 1995. Most participants were Caucasian, relatively well-educated, and from middle and upper socioeconomic strata. Participants were told the purpose of the study and provided their written informed consent to participate. The study protocol was approved annually by the Cooper Institute's institutional review board.

### 2.2. Baseline examination

After participants completed an overnight fast of at least 12 h, an extensive physical examination and preventive health evaluation were performed (Blair et al., 1989; Blair et al., 1996). During the examination, participants completed a maximal exercise treadmill test, provided blood for chemistry analyses, had measures of blood pressure taken, and responded to a comprehensive questionnaire that elicited demographic characteristics, personal health history, and lifestyle habits. Height and weight were measured on a standard physician's balance beam scale and stadiometer. Body mass index (BMI) was computed as weight (kg)/height $(m)^2$. Resting blood pressure was measured using standard auscultation methods after a brief period of quiet sitting. Blood chemistry was analyzed for lipids and glucose using standardized automated bioassays. The presence of hypertension and diabetes was determined based on a self-reported history of physician diagnosis or measured phenotypes that met clinical thresholds for each condition. Information on smoking habits (current smoker or not), alcohol intake (drinks per week), physician diagnosed mental disorder, and stressful occupation (yes or no) was obtained from a standardized questionnaire.

CRF was defined as the total time of a symptom-limited maximal treadmill exercise test, using a modified Balke protocol (Blair et al., 1989; Balke and Ware, 1959). Total time of the test on this protocol correlates highly with measured maximal oxygen uptake in both men (r = 0.92) (Pollock et al., 1976) and women (r = 0.94) (Pollock et al., 1982). The test endpoint was volitional exhaustion or termination by the supervising physician. Maximal metabolic equivalents (METs, 1 MET = 3.5 ml $O_2$ uptake$\cdot kg^{-1}\cdot min^{-1}$) were calculated from the final treadmill speed and grade.(American College of Sports Medicine, 2005) Previous ACLS reports have shown that low CRF is an independent predictor of mortality and morbidity (Blair et al., 1989; Blair et al., 1996; Sui et al., 2007). In previous ACLS reports, we have defined low, moderate, and high CRF exposures as the lowest 20% and the middle and upper 40%, respectively, of the age and sex-specific distribution of treadmill duration in the overall ACLS population (Sui et al., 2007). Abnormal exercise ECG responses were broadly defined as rhythm and conduction disturbances and ischemic ST-T wave abnormalities, as described in detail elsewhere (Gibbons et al., 2000). We have found 90% agreement between the ECG interpretation recorded in our database and that of a group of three physicians who read a random sample of 357 patient records and were blinded to the recorded interpretation (Gibbons et al., 2000).

### 2.3. Assessment of outcome

The presence of depressive symptoms was assessed using the 20-item version of the CES-D, a measurement of depressive mood experienced during the past week. This 20-item self-report scale is designed to measure depressive symptoms in the general population (Radloff, 1977). Although the CES-D is not a diagnostic instrument, it is a valid, reliable, and widely-used tool for screening and detecting depressive symptoms in the general population (Beekman et al., 1997; Cheung et al., 2007). The range of possible scores is 0–60, with higher scores indicating a higher degree of depressive symptoms. A CES-D score of 16 or higher is commonly interpreted as indicating the presence of depressive symptoms. This cutpoint has been used extensively in studies of the general population (Radloff, 1977), in studies of older subjects (Beekman et al., 1997; Heikkinen and Kauppinen, 2004), and also in studies that separately examined women and men (Ried and Planas, 2002). We used this cutpoint to define the presence of depressive symptoms. All participants completed the CES-D as part of a mail-back survey in 1990 and/or 1995. There were 10,190 and 9,674 participants who responded to the 1990 and 1995 surveys, respectively; 5,521 responded to both surveys. The aggregate survey response rate across these two survey periods was about 65%. Nonresponse bias is a concern in epidemiological surveillance. This issue has

been investigated in the ACLS (Macera et al., 1990). Baseline health histories and clinical measures were similar between responders and nonresponders, and between early and late responders (Macera et al., 1990). We also investigated whether differential mortality might have affected response rates, using the National Death Index to identify decedents. We found that mortality rates were similar for responders and nonresponders (unpublished data). In participants who replied to both surveys, the more recent depressive symptom score was used for analysis.

### 2.4. Statistical analysis

All analyses were sex-specific. Descriptive statistics were calculated for both women and men. We used logistic regression to evaluate the association between CRF and depressive symptoms. Multivariate analyses included 9 covariables: age (years), baseline examination year, current smoker (yes/no), alcohol intake (⩾5 drinks/wk, or less), abnormal exercise ECG responses (present or not), BMI, hypertension (present or not), and diabetes (present or not). To account for differences in survey response patterns among study participants, and for the possibility that external events may have differentially affected responses to the CES-D during the two survey periods, we created a dummy variable that indicated whether the outcome measurement was from 1990 or 1995. Incidence rates were calculated by dividing the number of individuals reporting elevated levels of depressive symptoms by the population at risk, both for the total sample and within categories of fitness. Tests of linear trend across CRF categories were conducted by entering the three-category fitness variable into the regression models as an ordinal term. To examine potential modifying effects of selective variables on the fitness-depressive symptoms association, we stratified data in the following groups: age (<65 vs. ⩾65 years), BMI (18.5–24.9 vs. 25.0–29.9 vs. ⩾30.0), current smoker, alcohol consumption, hypertension, and diabetes. All $p$ values are 2-sided with an alpha level of 0.05. All analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

## 3. Results

The mean baseline age of the study sample was 44.9 years (SD, 9.7); 22% were female. Baseline treadmill time ranged from 1.0 to 38.3 min, with a mean of 17.4 (SD, 5.4). Among the participants, the prevalence of low, moderate, and high CRF was 12.7% (1,816), 37.1% (5,317), and 50.3% (7,210), respectively. Time to follow-up averaged 12 years (range 1 to 25 years), with 174,554 total person-years of exposure. Among women, 9.1% reported depressive symptoms at follow-up (CES-D scores above 16). The corresponding rate for men was 6.6%. Table 1 presents characteristics of the women (n=3,085) and men (n=11,258) in the study.

Fig. 1A (representing men) and Fig. 1B (representing women) present unadjusted incidence rates of elevated depressive symptoms across low, moderate, and high categories of CRF. There was an inverse gradient for the incidence of depressive symptoms across incremental levels of CRF ($p_{trend} < 0.0001$, for both men and women).

Table 2 shows odds ratios (ORs) for depressive symptoms, and their associated 95% confidence intervals (CIs), adjusted for age, baseline examination year, and the survey response year. Each additional minute of treadmill test duration at baseline was associated with 5% lower odds of reporting depressive symptoms at follow-up, for both men and women (OR 0.95; CI 0.94–0.97 for men, 0.92–0.98 for women). The analogous adjusted OR for depressive symptoms associated with each additional MET of maximal energy expenditure was 0.91 (CI 0.88–0.94) in men, and 0.89 (CI 0.83–0.95) in women. The remaining data rows of Table 2 show comparable ORs and CIs associated with other risk factors in the analysis, all adjusted for the same set of potential confounders. For example, obese individuals had higher depressive symptoms risk in comparison with those of normal weight in both men (OR 1.55, CI 1.22–1.96) and women (OR 1.93, CI 1.11–3.35). Those with stressful occupations had higher depressive symptoms risk than others. Current smokers had higher depressive symptoms risk than noncurrent smokers (Table 2).

**Table 1**
Baseline characteristics of men and women, aerobics center longitudinal study, 1970–1995

| Characteristic | Men ($n$=11,258) | Women ($n$=3,085) |
|---|---|---|
| Age (years) | 45.0±9.5 | 44.6±10.3 |
| Maximal METs | 12.0±2.6 | 9.6±2.2 |
| Treadmill time (minutes) | 18.5±5.1 | 13.5±4.7 |
| Low fitness (%) | 12.9 | 11.8 |
| Moderate fitness (%) | 37.2 | 36.7 |
| High fitness (%) | 49.9 | 51.6 |
| Body Mass Index (kg/m$^2$) | 25.7±3.3 | 22.5±3.3 |
| Lipids (mmol/L) | | |
| Total cholesterol | 5.5±1.0 | 5.3±1.2 |
| HDL-C | 1.2±0.3 | 1.6±0.5 |
| Triglycerides | 1.4±1.0 | 1.0±1.1 |
| Fasting blood glucose (mmol/L) | 5.6±0.9 | 5.2±0.7 |
| Blood pressure (mmHg) | | |
| Systolic | 122±14 | 113±14 |
| Diastolic | 81±9 | 75±9 |
| Stressful occupation[a] (%) | 36.8 | 17.9 |
| Current smoker (%) | 13.4 | 8.8 |
| Alcohol intake (⩾5 drinks/week)[b] (%) | 41.7 | 25.1 |
| Hypertension[c] (%) | 24.1 | 12.3 |
| Diabetes[d] (%) | 4.1 | 1.9 |
| Abnormal exercise ECG (%) | 5.5 | 4.7 |

Data shown as Means ± SD unless specified otherwise.
METs = maximal metabolic equivalents achieved during the treadmill test; HDL-C = high density lipoprotein cholesterol; ECG = electrocardiogram.
[a] Defined as yes or no based on a standardized questionnaire
[b] One unit of alcohol is defined as 12 ounces (3.41 dl) of beer, 5 ounces (1.421 dl) of wine, or 1.5 ounces (0.4262 dl) of hard liquor.
[c] Hypertension is defined as systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg, or a history of physician diagnosis.
[d] Diabetes mellitus is defined as a fasting plasma glucose concentration ⩾7.0 mmol/L (126 mg/dl), a history of physician diagnosis, or insulin use.

Table 3 shows, separately for men and women, the number of study participants in each of the 3 CRF categories, the number of cases where respondents reported depressive symptoms at follow-up (events), and the ORs and CIs from 2 sets of logistic regression models focused on the 3 CRF categories. Model 1 adjusted for age, baseline examination year, and the year in which the participant completed the follow-up survey. In the results from Model 1, low CRF was a notable predictor of depressive symptoms for both women and men. Compared to women with low CRF, the odds of reporting depressive symptoms were 44% lower for women with moderate CRF (OR 0.56, CI 0.40–0.80), and 54% lower for women with high CRF (OR 0.46, CI 0.32–0.65, $p_{trend} < 0.0001$). Compared to men with low CRF, the odds of reporting depressive symptoms were 31% lower for men with moderate CRF (OR 0.69, CI 0.56–0.85) and 51% lower for men with high CRF (OR 0.49, CI 0.39–0.60, $p_{trend} < 0.0001$).

Model 2 of Table 3 further adjusts for stressful occupation, current smoking, alcohol consumption, body mass index, hypertension, diabetes, and abnormal exercise ECG responses. The results shown in Model 2 suggest only modest attenuation of the association between CRF and depressive symptoms with the additional controls for this larger set of potential confounders.

The associations between baseline CRF and the risks of reporting depressive symptoms at follow-up within categories of other possible risk factors are presented in Table 4. In men, after adjust-

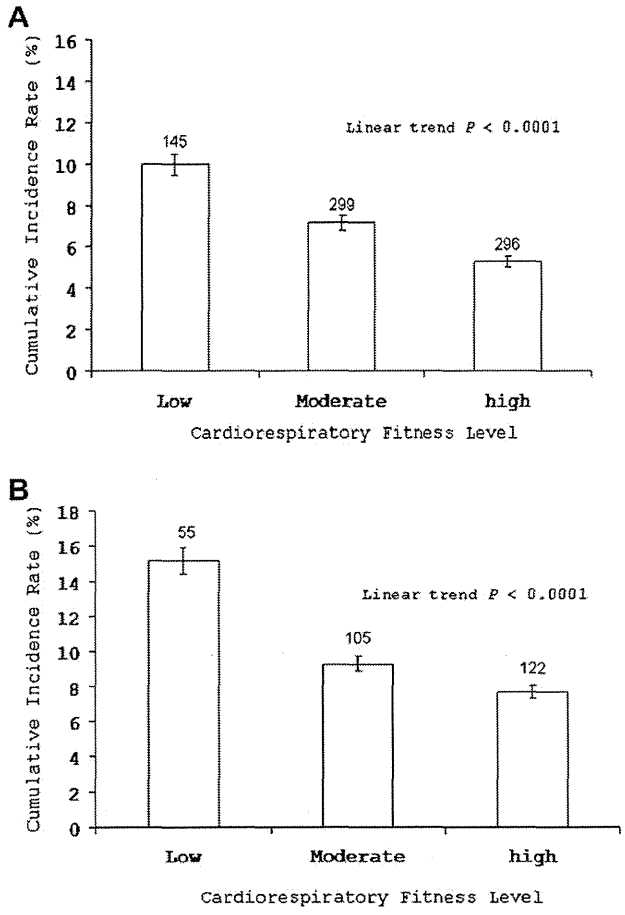


**Fig. 1.** Incidence of depressive symptoms by cardiorespiratory fitness categories among men **(1A)** and women **(1B)**. Bars indicate 95% confidence intervals. The number of cases is shown above the bars.

**Table 2**
Odds ratios (ORs)[a] for depressive symptoms, by study risk factors

| Variable | Men OR (95% CI) | Women OR (95% CI) |
|---|---|---|
| Treadmill test duration (per 1 min increment) | 0.95 (0.94–0.97) | 0.95 (0.92–0.98) |
| Treadmill test maximal METs (per 1-MET increment) | 0.91 (0.88–0.94) | 0.89 (0.83–0.95) |
| Body mass index, kg/m$^2$ | | |
| 18.5–24.9 | 1.00 (Referent) | 1.00 (Referent) |
| 25.0–29.9 | 1.14 (0.97–1.34) | 1.30 (0.91–1.85) |
| ⩾ 30.0 | 1.55 (1.22–1.96) | 1.93 (1.11–3.35) |
| *P*-linear trend | 0.0007 | 0.01 |
| Stressful occupation | 1.56 (1.34–1.82) | 1.31 (0.97–1.76) |
| Current smoker | 1.42 (1.16–1.72) | 1.23 (0.82–1.84) |
| Alcohol consumption (⩾5drinks/week) | 1.01 (0.87–1.18) | 1.00 (0.75–1.33) |
| Hypertension | 1.06 (0.89–1.27) | 1.11 (0.76–1.62) |
| Diabetes | 1.00 (0.68–1.47) | 1.80 (0.84–3.85) |
| Abnormal exercise ECG responses | 1.04 (0.73–1.46) | 1.14 (0.63–2.08) |

OR, odds ratio; CI, confidence interval. OR, odds ratio; CI, confidence interval; ECG, electrocardiogram; METs, metabolic equivalents.
[a] Adjusted for age, baseline examination year, and survey response year.

ing for age, baseline examination year, survey response year, and each of the other variables in the table, each additional MET of maximal exercise was, on average, associated with 4%–14% ($p < 0.05$) lower odds of reporting depressive symptoms in each risk factor group, adverse or not. The consistency in the direction and magnitude of association between CRF and depressive symptoms

**Table 3**
Risks for depressive symptoms, by level of cardiorespiratory fitness

| | N | Events | Model 1[a] OR | Model 1[a] 95% CI | Model 2[b] OR | Model 2[b] 95% CI |
|---|---|---|---|---|---|---|
| Men | | | | | | |
| Cardiorespiratory fitness | | | | | | |
| Low | 1453 | 145 | 1.00 | Referent | 1.00 | Referent |
| Moderate | 4186 | 299 | 0.69 | 0.56-0.85 | 0.73 | 0.58-0.91 |
| High | 5619 | 296 | 0.49 | 0.39-0.60 | 0.53 | 0.42-0.68 |
| *P*-linear trend | | | | <0.0001 | | <0.0001 |
| Women | | | | | | |
| Cardiorespiratory fitness | | | | | | |
| Low | 363 | 55 | 1.00 | Referent | 1.00 | Referent |
| Moderate | 1131 | 105 | 0.56 | 0.40–0.80 | 0.60 | 0.42–0.87 |
| High | 1591 | 122 | 0.46 | 0.32–0.65 | 0.51 | 0.34–0.75 |
| *P*-linear trend | | | | <0.0001 | | 0.002 |

OR=odds ratio; CI=confidence interval; ECG=electrocardiogram.
[a] Adjusted for age, baseline examination year and survey response year.
[b] Adjusted for the above plus stressful occupation (yes or no), current smoking (yes or no), alcohol consumption (⩾ 5 drinks/week or not), body mass index, hypertension, diabetes (present or not for each), and abnormal exercise ECG responses (present or not).

suggested that there was little effect modification across risk factor categories. In women, the pattern of association between CRF and depressive symptoms was less consistent across risk factors, although in all instances the point estimates for the ORs were below 1.0. The somewhat larger variation among the point estimates for women, and the marginal statistical significance in many instances, may be attributable to a small number of events in many categories, and limited statistical power. Given the smaller number of women in the sample, it is also possible that the sample size for women may not have been sufficient to provide stable estimates.

## 4. Discussion

### 4.1. Principal findings

In longitudinal analyses, we found a sharply graded inverse dose-response relationship between CRF at baseline and depressive symptoms at follow-up, in both men and women. Participants with low CRF were at significantly greater risk of developing depressive symptoms, even after adjustment for age, baseline examination year, follow-up survey response year, smoking status, alcohol consumption, body mass index, hypertension, diabetes, and abnormal exercise ECG responses. The inverse association between CRF and depressive symptoms was generally consistent within strata of other potential risk factors.

The findings that obese men and women had significantly higher risk of depressive symptoms are consistent with other studies. Recently, Petry et al studied 41,654 participants and found that obesity was associated with significantly increased odds of major depression compared with normal weight individuals (Petry et al., 2008). It is becoming more evident that there may be a relationship between BMI and depressive symptoms. Future studies will be warranted to provide more evidence in this area.

### 4.2. Possible mechanisms of action

The precise physiological mechanisms associating physical activity with depression are not well established. Some possible explanations are proposed. Neuroscientific evidence suggests that exercise can increase the release of brain neurotransmitters such as monoamines and endorphins (Morgan, 1985; Thoren et al., 1990) or brain-derived neurotrophic factor (Zheng et al., 2006; Russo-Neustadt et al., 2000), which inhibit cell death and provide

**Table 4**
Odds ratios for depressive symptoms per 1-MET increment in maximal exercise test, by study risk factors[a]

| Risk Factor | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Events | OR | 95% CI | N | Events | OR | 95% CI |
| Age, years[b] | | | | | | | | |
| <55 | 9380 | 621 | 0.88 | 0.80–0.97 | 2523 | 238 | 0.95 | 0.88–1.02 |
| ⩾55 | 1878 | 119 | 0.96 | 0.92–1.00 | 562 | 44 | 0.86 | 0.69–1.07 |
| Body mass index, kg/m$^2$[b] | | | | | | | | |
| 18.5-24.9 | 5268 | 317 | 0.94 | 0.89–0.99 | 2592 | 226 | 0.91 | 0.84–0.99 |
| 25.0-29.9 | 4889 | 326 | 0.91 | 0.85–0.97 | 385 | 40 | 0.93 | 0.73–1.18 |
| ⩾30 | 1101 | 97 | 0.86 | 0.75–0.99 | 108 | 16 | 0.61 | 0.35–1.04 |
| Stressful occupation[b] | | | | | | | | |
| No | 7113 | 390 | 0.94 | 0.89–0.99 | 2534 | 220 | 0.94 | 0.87–1.02 |
| Yes | 4145 | 350 | 0.91 | 0.86–0.96 | 551 | 62 | 0.78 | 0.65–0.93 |
| Current smoker[b] | | | | | | | | |
| No | 9746 | 609 | 0.94 | 0.90–0.98 | 2814 | 252 | 0.91 | 0.84–0.99 |
| Yes | 1512 | 131 | 0.87 | 0.78–0.96 | 271 | 30 | 0.85 | 0.63–1.05 |
| Alcohol consumption[b] | | | | | | | | |
| <5 drinks/week | 6560 | 427 | 0.94 | 0.89–0.99 | 2312 | 210 | 0.92 | 0.84–1.00 |
| ⩾5 drinks/week | 4698 | 313 | 0.90 | 0.97–0.995 | 773 | 72 | 0.87 | 0.74–1.01 |
| Hypertension[b] | | | | | | | | |
| No | 8541 | 560 | 0.93 | 0.89–0.97 | 2707 | 247 | 0.93 | 0.86–1.00 |
| Yes | 2717 | 180 | 0.91 | 0.83–0.99 | 378 | 35 | 0.73 | 0.87–0.96 |
| Diabetes[b] | | | | | | | | |
| No | 10,795 | 711 | 0.93 | 0.89–0.97 | 3028 | 274 | 0.91 | 0.84–0.98 |
| Yes | 463 | 29 | 0.87 | 0.70–1.09 | 57 | 8 | 0.92 | 0.50–1.68 |

OR, odds ratio; CI, confidence interval.
[a] The point and interval estimates represent the relative odds of reporting depressive symptoms at follow-up that are associated, on average, with each 1-MET increment in the baseline treadmill exercise test.
[b] Adjusted for baseline examination year, survey response year, and each of the other risk factors in the table.

antidepressant effects. Other plausible mechanisms focus on psychosocial factors such as self-esteem (Stewart et al., 1994), social interaction (Peluso and Guerra de Andrade, 2005), and a sense of ownership (Stephens, 1988), which could result from improved fitness and may affect mental health and mood Comparison with other published studies.

The prospective results of the current study are consistent with previous follow-up studies that have suggested an inverse association between physical activity and depressive disorder not only in younger and middle-aged persons (Farmer et al., 1988; Camacho et al., 1991; Paffenbarger et al., 1994), but also in older men and women (Strawbridge et al., 2002; Kritz-Silverstein et al., 2001). Only a limited number of previous studies have objectively measured CRF (Thirlaway and Benton, 1992; Galper et al., 2006; Tolmunen et al., 2006). These studies have inconsistent findings, and are all limited by cross-sectional designs. Thirlaway and Benton did not find a relationship between CRF and depression in active individuals (Thirlaway and Benton, 1992), while the most recent two studies did report lower rates of depressive symptoms in persons with higher levels of CRF (Galper et al., 2006; Tolmunen et al., 2006). In the ACLS, Galper et al. (2006) found that both women and men had lower mean CES-D scores across higher fitness levels after adjustment for age, BMI, and years of participation in physical activity. In a group of middle-aged men from the Kuopio Ischemic Heart Disease Risk Factor study, (Tolmunen et al., 2006) observed that men with low oxygen uptake (less than 28.1 ml/kg/min) had a 3.4-fold higher risk of being depressed, compared with those with a $VO_{2max}$ exceeding 36.2 ml/kg/min. Furthermore, they reported a correlation between the severity of the depression scores and levels of fitness (Tolmunen et al., 2006). To our knowledge, the present study is the first to explore the association between CRF and depressive symptoms in longitudinal analysis. Future follow-up studies are needed to confirm our findings.

### 4.3. Strengths and limitations

The main strength of the current study is its use of maximal exercise testing to quantify CRF. CRF is considerably less prone to misclassification than other measures of physical activity. It may better reflect the adverse health consequences of a sedentary lifestyle than self-reported physical activity (Haskell et al., 1992). Thus, our approach improves on previous population-based studies, which have generally relied on self-reported measures of physical activity (Wiles et al., 2007; Paffenbarger et al., 1994; Farmer et al., 1988; Camacho et al., 1991). Second, we used measured risk factors and validated instruments to determine depressive symptoms. Third, the large number of person-years of follow-up enabled us to investigate dose-response effects in both men and women, and within categories of other exposures. Fourth, we accounted for variable patterns of survey responses in our analyses, an approach not usually used in cohort studies such as ours (Wiles et al., 2007). Finally, we excluded individuals with cancer, cardiovascular disease, or a self-report of having had a physician diagnosis of any mental disorder at baseline, reducing the likelihood of residual confounding. It is possible that participants with low CRF at baseline had high CES-D scores at baseline, which will underestimate the true association. The sociodemographic homogeneity of our study participants should enhance the internal validity of our findings, by reducing the likelihood of notable confounding by factors such as education, income, occupational and residential characteristics, prestige, and lifestyle. The self-referred origin and homogeneity of our cohort may be seen as a limitation. However, the ACLS study group is similar in many respects to other cohorts that have provided important information on disease prevention (Paffenbarger et al., 1994; Lee and Paffenbarger, 1998).

Nonetheless, generalizations to other adult populations should be made with caution. CES-D scores were not available at baseline. For that reason, we excluded those who reported having been clinically diagnosed with mental health disorders or chronic diseases, providing a degree of control for initial level of mental health. It should be recognized that relying on self-reports of previous diagnoses may introduce measurement error into the analysis. However, we have found in previous analyses that the sensitivity and specificity of self-report of other health problems in this cohort are quite high. For example, the percentage of agreement between

self-reported events and participants' medical records was 88%, 100%, 89% for myocardial infarction, revascularization, and stroke, respectively (Sui et al., 2007). We previously also verified the accuracy of self-reported, physician-diagnosed hypertension in this cohort and observed 98% sensitivity and 99% specificity (Blair et al., 1984). We did not use clinical diagnostic criteria to diagnose depression. Some of the study participants who were classified as having depressive symptoms might not have qualified for the diagnosis of clinical depression. It is also possible that the CES-D cut-point of 16 may be too low, in which case our outcome variable would mis-classify some individuals, as false positives. There is no widely accepted "optimal" cut-off score for the CES-D (Cheung et al., 2007).

Studies of the validity of the CES-D for identifying symptoms associated with major depressive disorder in adults have suggested a range of optimal scores for screening, generally ranging from 16 to 25 (Parikh et al., 1988; Lyness et al., 1997; Haringsma et al., 2004; Wada et al., 2007). A recent detailed study of the performance of the CES-D for screening for major depression in cancer patients identified the optimal cut-off score of 17, which was associated with 100% sensitivity, 79% specificity, and 92% positive predictive value (Hopko et al., 2008); thus, this score missed no cases of clinical depression, and correctly identified 79% of those without depression, while only 8% of those screening positive would not be clinically diagnosed with major depression. Nonetheless, we stress that case-finding tools such as the CES-D were not developed to make clinical diagnoses. Although results from the CES-D are commonly used for outcome measurement in epidemiological studies, this tool was developed primarily to identify individuals with clinically significant symptoms that require more intensive evaluation. We therefore advise caution when interpreting the results of this study. To examine the sensitivity of the cut-point used in this analysis, we conducted additional analyses using cut-points of 20 and 24 to define depressive symptoms. In these sensitivity analyses, the association between CRF and the depressive symptoms outcome was not materially changed (data not shown). The findings of our study also may be affected by unmeasured factors related to fitness and/or depressive symptoms, although it seems unlikely that such factors would explain all of the observed association between CRF and depressive symptoms. We do not have sufficient information on medication use, treatments, menopausal status, pregnancy status, or dietary habits to include these factors in our analysis. Such information should be included in future studies, to expand on the findings reported here.

### 4.4. Implications of the current study

We computed population attributable risk (Rothman and Greenland, 1998) values to estimate the burden of depressive symptoms attributable to low fitness and other risk predictors. If all individuals with low fitness in our population sample became fit, the incidence of depressive symptoms cases might have been 7% and 9% lower in men and women, respectively (data not shown). Currently, there is not enough data to determine how much of the depressive symptoms burden may be due to low fitness. These findings from the ACLS cohort suggest that assessing and possibly increasing population fitness levels should be given consideration for primary prevention and for lowering the burden of depressive symptoms through lifestyle changes such as increasing physical activity. CRF can be enhanced through participation in moderate and vigorous physical activities, such as brisk walking, bicycling, and jogging for 30 min or more on most days of the week (Pate et al., 1995). Our recent randomized trial showed a significant improvement in $VO_{2max}$ in overweight or obese postmenopausal women with as little as 72 min of moderate intensity physical activity/week (Church et al., 2007). The clear dose-response relationship between fitness and depressive symptoms found in the current study should encourage individuals to lead a physically active lifestyle. Doing so may reduce not only cardiovascular disease, the leading cause of death in the United States, but also the risk of depression. These findings are also helpful for health care professionals. They suggest the usefulness of advising sedentary patients about the benefits of physical activity for mental well-being.

### 4.5. Conclusions

In a large sample of men and women, this prospective study showed that CRF is inversely associated with the risk of developing elevated depressive symptoms. This result is consistent with previous longitudinal studies of self-reported physical activity and depressive symptoms. Further studies are needed to expand our findings on functional capacity assessment using exercise testing to clinically defined depression in the general population.

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## References

American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. Philadelphia: Lippincott Williams and Wilkins; 2005.
Balke B, Ware RW. An experimental study of physical fitness in Air Force personnel. US Armed Forces Medical Journal 1959;10:675–88.
Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression Scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychology Medicine 1997;27:231–5.
Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. Journal of the American Medical Association 1984;252:487–90.
Blair SN et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. Journal of the American Medical Association 1996;276:205–10.
Blair SN, Kohl III HW, Paffenbarger Jr RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. Journal of the American Medical Association 1989;262:2395–401.
Blumenthal JA et al. Effects of exercise training on older patients with major depression. Archieves of International Medicine 1999;159:2349–56.
Bouchard C, Blair SN, Haskell WL. Physical activity and health. Human kinetics, Inc.;
.
Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD. Physical activity and depression: evidence from the Alameda County Study. American Journal of Epidemiology 1991;134:220–31.
Cheung YB, Liu KY, Yip PS. Performance of the CES-D and its short forms in screening suicidality and hopelessness in the community. Suicide Life-Threat Behav 2007;37:79–88.
Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. Journal of the American Medical Association 2007;297:2081–91.
Cooper-Patrick L, Ford DE, Mead LA, Chang PP, Klag MJ. Exercise and depression in midlife: a prospective study. American Journal of Public Health 1997;87:670–3.
Druss BG, Rosenheck RA, Sledge WH. Health and disability costs of depressive illness in a major US corporation.. American Journal of Psychiatry 2000;157:1274–8.
Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. Medicine and Science in Sports Exercise 2001;33:S587–97.
Farmer ME, Locke BZ, Moscicki EK, Dannenberg AL, Larson DB, Radloff LS. Physical activity and depressive symptoms: the NHANES I Epidemiologic Follow-up Study. American Journal of Epidemiology 1988;128:1340–51.
Galper DI, Trivedi MH, Barlow CE, Dunn AL, Kampert JB. Inverse association between physical inactivity and mental health in men and women. Medicine and Sciene in Sports and Exercise 2006;38:173–8.
Gibbons LW, Mitchell TL, Wei M, Blair SN, Cooper KH. Maximal exercise test as a predictor of risk for mortality from coronary heart disease in asymptomatic men. American Journal of Cardiology 2000;86:53–8.
Green RC et al. Depression as a risk factor for Alzheimer disease: the MIRAGE study. Archieves of Neurology 2003;60:753–9.