Exercise Capacity and Risk of Chronic Kidney Disease in US Veterans: A Cohort Study

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Abstract

Objective: To assess the association between exercise capacity and the risk of developing chronic kidney disease (CKD).

Patients and Methods: Exercise capacity was assessed in 5812 male veterans (mean age, 58.4±11.5 years) from the Veterans Affairs Medical Center, Washington, DC. Study participants had an estimated glomerular filtration rate of 60 mL/min per 1.73 m² or more 6 months before exercise testing and no evidence of CKD. Those who developed CKD during follow-up were initially identified by the International Classification of Diseases, Ninth Revision and further verified by at least 2 consecutive estimated glomerular filtration rate values of less than 60 mL/min per 1.73 m² 3 months or more apart. Normal kidney function for CKD-free individuals was confirmed by sequential normal eGFR levels. We established 4 fitness categories on the basis of age-stratified quartiles of peak metabolic equivalents (METs) achieved: least-fit (≤25%; 4.8±0.90 METs; n=1258); low-fit (25.1%-50%; 6.5±0.96 METs; n=1614); moderate-fit (50.1%-75%; 7.7±0.91 METs; n=1958), and high-fit (≥75%; 9.5±1.0 METs; n=1436). Multivariable Cox proportional hazard models were used to assess the association between exercise capacity and CKD.

Results: During a median follow-up period of 7.9 years, 1010 developed CKD (20.4/1000 person-years). Exercise capacity was inversely related to CKD incidence. The risk was 22% lower (hazard ratio, 0.78; 95% CI, 0.75-0.82; P<.001) for every 1-MET increase in exercise capacity. Compared with the least-fit individuals, hazard ratios were 0.87 (95% CI, 0.74-1.03) for low-fit, 0.55 (95% CI, 0.47-0.65) for moderate-fit, and 0.42 (95% CI, 0.33-0.52) for high-fit individuals.

Conclusion: Higher exercise capacity attenuates the risk of developing CKD. The association was independent and graded.
PATIENTS AND METHODS

Design and Sampling
This prospective cohort study included individuals from a larger database, established at the Veterans Affairs Medical Center in Washington, DC, to assess the association between exercise capacity and health outcomes in veterans. All participants (n=7733) had a symptom-limited exercise test between January 12, 1987, and December 30, 2012. The test was administered either as part of a routine assessment, clearance to participate in exercise, or to assess exercise-induced ischemia. In case of multiple exercise tests, the first test was used.

From this database, we excluded individuals without eGFR data or an eGFR of less than 60 mL/min per 1.73 m² before the exercise test (n=898). We also excluded all women (n=454) and those with the following conditions at the time of the exercise test: (1) body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) of less than 18.5 kg/m², to minimize the potential effect of low body weight on mortality due to cachexia (n=116); (2) an exercise capacity of less than 2 metabolic equivalents (METs), unable to complete the test, or required emergent intervention (n=185); (3) those with an implanted pacemaker (n=145); (4) those with chronic failure New York Heart Association class II or higher (n=58); and (5) those with chronic obstructive pulmonary disease (n=65). After these exclusions, the cohort comprised 5812 participants (mean age, 58.4±11.5 years). Of these, 4287 (73.8%) were black (mean age, 58.0±11.3 years) and 1525 (26.2%) were white (mean age, 59.5±12.0 years).

CKD Determination
Preexercise eGFR (baseline eGFR) was estimated for each participant, using serum creatinine measurements performed within 6 months before the exercise test, available in the electronically stored medical records known as the Computerized Patient Record System (CPRS). When more than 1 serum creatinine measurement was available, the one carried out closest to the exercise test was used. Participants who developed CKD during the follow-up period were initially identified by using the International Classification of Diseases, Ninth Revision (ICD-9) and further verified with at least 2 consecutive eGFR values of less than 60 mL/min per 1.73 m² 3 months or more apart. Follow-up eGFR level for these individuals was estimated on the basis of serum creatinine measurements at the time CKD diagnosis was recorded. Normal kidney function for those who did not develop CKD was confirmed by sequential normal eGFR levels. Follow-up eGFR was assessed using the last available serum creatinine measurement. All eGFR values were estimated by using the Chronic Kidney Disease Epidemiology Collaboration equation. The study was approved by the institutional review board of the Veterans Affairs Medical Center, Washington, DC, and all subjects gave written informed consent before their exercise test.

Details on relevant demographic, clinical, and medication information, risk factors, and comorbidities as defined by the ICD-9 coding for all participants were obtained from the CPRS at the time of the exercise test. Body weight and height were assessed using a standardized scale and recorded before the test and the BMI was calculated. In addition, risk factors and comorbidities as defined by the ICD-9 coding for all participants were recorded from electronic medical records.

Exercise-Related Assessments
Cardiorespiratory fitness was assessed by a standard treadmill test using the Bruce protocol. Peak exercise capacity (in METs) was estimated using standardized equations. One MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL of O₂ per kg body weight per minute. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping. The use of handrails was allowed only if necessary for balance and safety. Medications were not altered before testing.

We stratified the cohort into 3 age categories: younger than 50 years, 50 to 69 years, and 70 years or older. We then identified those with a MET level of 25% or less, more than 25% to 50%, more than 50% to 75%, and more than 75% of METs achieved within their respective age category, as described previously. We then established the following 4 fitness categories on the basis of age-stratified quartiles of peak METs achieved: least-fit category (4.8±0.90 METs;...
EXERCISE CAPACITY AND CHRONIC KIDNEY DISEASE

Follow-up and End Point

The study end point was the development of CKD (stages 3-5), as diagnosed and recorded electronically (the CPRS) by a physician. Vital status was determined as of December 31, 2013.

Statistical Analyses

Follow-up time was calculated from the date of the exercise test to the date of death for the decedents, and to December 31, 2013, for those who survived. The CKD rate was calculated as the ratio of the number of deaths divided by the number of person-years. Continuous variables were presented as mean values ± SD, and categorical variables were presented as relative frequencies (%). Comparisons between categorical variables were assessed using the chi-square test. Simple linear regression was applied to evaluate differences between fitness categories and age. Multivariable linear regression was used to evaluate differences between fitness categories and BMI, resting heart rate, systolic blood pressure (BP), and body weight (dependent variables), adjusted for age. Differences between fitness categories for baseline eGFR and peak MET level achieved (dependent variables) were also assessed, adjusting for age, resting systolic BP, and BMI, variables known to affect the dependent variable. The independent Student t test was used to compare baseline eGFR values between those who did and did not develop CKD. The paired t test was also used to assess within-group differences between baseline and follow-up eGFR. The assumption of equality of variances between groups was tested by using the Levene test.

Multivariable Cox proportional hazards regression models were then used to evaluate the association between the fitness categories (using the least-fit category as the reference group) and the development of moderate to severe CKD (stages 3-5). In the fully adjusted model, the covariates were age, baseline eGFR, BMI, CVD, race, cardiovascular risk factors, including hypertension, diabetes mellitus (DM), dyslipidemia, sleep apnea, history of alcohol abuse and history of smoking (defined as either smoker at the time of the exercise test or cessation of smoking <1 year before the exercise test), cardiohypertension medications (β-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers), and lipid-lowering and hypoglycemic agents. All variables included in the models were based on the rationale of their clinical role in the outcome and the main factors of interest. The assumption of proportionality for the Cox proportional hazards models was graphically tested by plotting the logarithm of the cumulative hazards with time for each covariate; the proportionality assumption was fulfilled for each model. Interaction between race and fitness status was tested in the fully adjusted Cox model by using the Wald test in SPSS by entering the interaction term race by MET (continuous variable) in the fully adjusted Cox model. Interaction between race and fitness categories (least-fit, low-fit, moderate-fit, and high-fit) was also assessed by entering the interaction term race by fitness categories in the fully adjusted Cox model. All hypotheses tested were 2 sided, and P values of less than .05 were considered statistically significant. All statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows, Version 22.0).

RESULTS

For the 5812 participants included in the analysis, the mean age at the time of the exercise test was 58.4±11.5 years. All participants had no diagnosis of CKD in their medical records at the time of the exercise test, and all had an eGFR of 60 mL/min per 1.73 m² or more. The follow-up time ranged from 0.5 to 24.8 years (mean, 8.0±4.4 years). The median was 7.9 years (4.4 and 11.7 for 25th and 75th percentiles, respectively), comprising a total of 46,697.2 person-years.

There were 1000 individuals who developed CKD (17.2%) with an average annual CKD rate of 21.4 events per 1000 person-years. Baseline eGFR levels were significantly higher for those who did not develop CKD than for those who did (98.2±16.8 mL/min per 1.73 m² vs 88.3±17.0 mL/min per 1.73 m²; P<.001). Thus, baseline eGFR...
TABLE 1. Demographic and Clinical Characteristics for the Entire Population and According to Fitness Categories

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire cohort (N=5812)</th>
<th>Least-fit (n=1133)</th>
<th>Low-fit (n=1458)</th>
<th>Moderate-fit (n=1831)</th>
<th>High-fit (n=1390)</th>
<th>P value (for trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58.4±1.1</td>
<td>61.7±1.1</td>
<td>59.4±1.3</td>
<td>58.4±1.2</td>
<td>54.6±1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.1±1.8</td>
<td>98.0±2.0</td>
<td>96.3±2.0</td>
<td>92.4±1.6</td>
<td>86.7±1.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.6±5.4</td>
<td>31.2±6.6</td>
<td>30.6±5.6</td>
<td>29.4±4.7</td>
<td>27.6±4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min per 1.73 m²)</td>
<td>96.5±1.6</td>
<td>94.9±1.7</td>
<td>96.4±1.7</td>
<td>96.5±1.7</td>
<td>97.9±1.6</td>
<td>.38</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>71.4±1.6</td>
<td>76.5±2.5</td>
<td>72.8±1.3</td>
<td>70.3±1.2</td>
<td>67.1±1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>124.8±18.2</td>
<td>130.4±19.1</td>
<td>126.6±17.6</td>
<td>123.2±16.8</td>
<td>120.9±18.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>76.9±17.0</td>
<td>77.6±12.0</td>
<td>77.4±20.2</td>
<td>76.8±20.5</td>
<td>76.0±10.5</td>
<td>.06</td>
</tr>
<tr>
<td>Exercise capacity (MET)</td>
<td>7.2±1.9</td>
<td>4.8±0.9</td>
<td>6.4±0.9</td>
<td>7.7±0.9</td>
<td>9.5±1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>1973 (33.9)</td>
<td>500 (44.1)</td>
<td>538 (36.9)</td>
<td>572 (31.2)</td>
<td>363 (26.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>1446 (25.2)</td>
<td>330 (29.1)</td>
<td>389 (26.7)</td>
<td>461 (25.2)</td>
<td>284 (20.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1807 (31.1)</td>
<td>502 (44.3)</td>
<td>548 (37.6)</td>
<td>508 (27.7)</td>
<td>249 (17.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1324 (22.8)</td>
<td>287 (25.3)</td>
<td>372 (25.5)</td>
<td>420 (22.9)</td>
<td>245 (17.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3762 (64.7)</td>
<td>886 (78.2)</td>
<td>1035 (71.0)</td>
<td>1179 (64.4)</td>
<td>662 (47.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypoglycemic agents, n (%)</td>
<td>930 (16.0)</td>
<td>270 (23.8)</td>
<td>280 (19.2)</td>
<td>257 (14.0)</td>
<td>123 (8.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac/antihypertensive agents, n (%)</td>
<td>3435 (59.1)</td>
<td>803 (70.9)</td>
<td>958 (65.7)</td>
<td>1070 (58.4)</td>
<td>604 (43.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE-I/ARBs, n (%)</td>
<td>1945 (32.7)</td>
<td>479 (42.3)</td>
<td>568 (39.0)</td>
<td>587 (32.1)</td>
<td>311 (24.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lipid-lowering agents, n (%)</td>
<td>1451 (25.0)</td>
<td>321 (28.3)</td>
<td>430 (29.5)</td>
<td>427 (23.3)</td>
<td>273 (19.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

aACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CCB = calcium-channel blocker; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; MET = metabolic equivalent.

Values are mean ± SD unless otherwise indicated.

βBlocks, diuretics, CCBs, ACE-I, ARBs, vasodilators.

was used as a covariate in the Cox proportional hazard model. Within-group comparisons for baseline and follow-up eGFR (paired t test) revealed that follow-up eGFR for individuals who developed CKD was lower (37.0±15.0 mL/min per 1.73 m² vs 88.3±17.0 mL/min per 1.73 m² for follow-up and baseline eGFR, respectively; P<.001). Similar findings were observed for individuals who did not develop CKD (88.3±17.0 mL/min per 1.73 m² vs 98.2±16.75 mL/min per 1.73 m² for follow-up and baseline eGFR, respectively; P<.001). There were no interactions between race and peak MET achieved (P=.71) or race and fitness categories (P=.28). Therefore, data were not stratified by race. In the fully adjusted model, exercise capacity when treated as a continuous variable (METs) was inversely related to the rate of developing CKD. For every 1-MET increase in exercise capacity when treated as a continuous variable (METs) was inversely related to the rate of developing CKD. For every 1-MET increase in exercise capacity when treated as a continuous variable (METs) was inversely related to the rate of developing CKD. For every 1-MET increase in exercise capacity (hazard ratio, 1.38; 95% CI, 1.16-1.63; P<.001). Additional independent predictors of CKD risk in the fully adjusted model were age (hazard ratio per year, 1.02; 95% CI, 1.01-1.03; P<.001), baseline eGFR (hazard ratio, 0.99; 95% CI, 0.98-0.99; P<.001), DM (hazard ratio, 1.38; 95% CI, 1.17-1.63; P<.001), hypertension (hazard ratio, 1.32; 95% CI, 1.08-1.63; P<.001), dyslipidemia (hazard ratio, 1.38; 95% CI, 1.16-1.63; P<.001).
populations, little is known about the association and high fitness have been described extensively in other settings. Therefore, we hypothesized that improved metabolic and cardiovascular profiles might exert a protective effect on renal function over time. The dose-response association between increased exercise capacity and protection against the development of CKD supports the likelihood that a causal mechanism may exist. Although the precise mechanisms that may underlie this effect are not known, a number of potential mechanisms may be involved. For example, as indicated in Table 1, our cohort included a significant number of patients with an elevated BMI and DM, conditions associated with insulin resistance, which, in turn, is associated with decreased insulin-stimulated vasodilation, capillary recruitment, and nutritive muscle blood flow and decreased exercise capacity. One explanation would suggest that individuals with a progressive reduction in the GFR may be deficient in vascular density and recruitment. Moreover, overweight and obese patients are more likely to develop cardiorenal metabolic syndrome, which not only includes insulin resistance but also dyslipidemia and hypertension, which contribute to vascular stiffness, and low-grade systemic inflammatory response, which sets the stage for heightened risk of CVD and CKD.

If metabolic factors play a role in the association between poor exercise capacity and the development of CKD, it is reasonable to hypothesize that improved metabolic and cardiovascular profiles exert a protective effect on renal function over time. The

**DISCUSSION**

The findings of the present study support an inverse, independent, and graded association between the development of CKD stage 3 or higher and exercise capacity. The decline in risk was precipitous with only modest increases in exercise capacity. Specifically, compared with the least-fit category (average peak exercise capacity 4.8 METs), the risk of developing CKD was 45% and 58% lower for individuals in the moderate and high-fit categories, respectively (Table 2).

Although the health benefits of increased fitness have been described extensively in other populations, little is known about the association between increased exercise capacity and the development of CKD. The findings of the few available studies suggest a direct association between physical inactivity and CKD prevalence whereas even light physical activity was positively associated with kidney function. In subjects with established CKD, higher physical activity was associated with slower rates of eGFR decline and higher gait speed and hand grip strength were associated with lower risk of death in 347 individuals followed for 3 years.

**TABLE 2. Hazard Ratios for Developing CKD According to Fitness Categories**

<table>
<thead>
<tr>
<th>Fitness categories</th>
<th>No. of events (%)</th>
<th>Hazard ratio (age-adjusted)</th>
<th>Hazard ratio (adjusted for age and BMI)</th>
<th>Hazard ratio (fully adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-fit (4.8±0.9 METs; n=1133)</td>
<td>313 (27.6)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Low-fit (6.5±1.0 METs; n=1458)</td>
<td>297 (20.4)</td>
<td>0.86 (0.73-1.01)</td>
<td>0.87 (0.74-1.02)</td>
<td>0.87 (0.74-1.03)</td>
</tr>
<tr>
<td>Moderate-fit (7.7±0.9 METs; n=1831)</td>
<td>268 (14.6)</td>
<td>0.54 (0.46-0.64)</td>
<td>0.55 (0.47-0.65)</td>
<td>0.55 (0.47-0.66)</td>
</tr>
<tr>
<td>High-fit (9.5±1.0 METs; n=1390)</td>
<td>122 (8.8)</td>
<td>0.37 (0.30-0.45)</td>
<td>0.38 (0.31-0.47)</td>
<td>0.42 (0.33-0.52)</td>
</tr>
</tbody>
</table>

**Hazard ratio**

- **Hazard ratio (age-adjusted)**
- **Hazard ratio (adjusted for age and BMI)**
- **Hazard ratio (fully adjusted)**

**Notes:**

- **ACE-I:** angiotensin-converting enzyme inhibitor; **ARB:** angiotensin receptor blocker; **BMI:** body mass index; **CKD:** chronic kidney disease; **CVD:** cardiovascular disease; **DM:** diabetes mellitus; **eGFR:** estimated glomerular filtration rate; **MET:** metabolic equivalent.

- Adjusted for age, baseline eGFR, BMI, race, and history of alcohol abuse, sleep apnea, CVD, dyslipidemia, hypertension, and DM.

- **Category 1:** Least-fit (4.8±0.9 METs; n=1133) 297 (20.4) 0.86 (0.73-1.01) 0.87 (0.74-1.02) 0.87 (0.74-1.03)
- **Category 2:** Low-fit (6.5±1.0 METs; n=1458) 268 (14.6) 0.54 (0.46-0.64) 0.55 (0.47-0.65) 0.55 (0.47-0.66)
- **Category 3:** Moderate-fit (7.7±0.9 METs; n=1831) 122 (8.8) 0.37 (0.30-0.45) 0.38 (0.31-0.47) 0.42 (0.33-0.52)
- **Category 4:** High-fit (9.5±1.0 METs; n=1390) 1 (1) 1 1 1
protective effects of increased cardiorespiratory fitness on renal function may also extend beyond the favorable modulation of metabolic and cardiovascular risk factors. Regular exercise affects structural and functional adaptations of the endothelial response to vasoconstrictors and vasodilators and may increase the sensitivity of the vasculature to vasodilating peptides. Consequently, physically active individuals have a greater capacity for capillary recruitment during exercise. In the kidney, this likely corresponds to an increased renal reserve, leading to a lower likelihood of developing CKD.

The findings of the present study demonstrate that health benefits associated with higher exercise capacity also extend to lowering the risk of developing CKD. Because moderate intensity exercise programs are effective in improving cardiorespiratory fitness regardless of age or comorbidities, we propose that exercise interventions for individuals at risk for CKD and those with preclinical CKD may be implemented to prevent or at least attenuate the rate of developing CKD. Clinical trials would be needed to confirm the effects of regular exercise on individuals with or at risk for CKD.

Study Strengths and Limitations
This study has several unique strengths and limitations. First, this is the first and largest study of its kind with more than 5800 individuals without evidence of existing kidney disease (eGFR > 60 mL/min per 1.73 m²) at baseline. Second, CKD incidence was established during a follow-up period of approximately 25 years. Third, fitness status (exercise capacity) of all participants was assessed objectively by an exercise test. Fourth, we had access to longitudinal data of serum creatinine and adjusted for important covariates including medications and established cardiovascular disease and CKD risk factors. Finally, the equal access to care independent of a patient’s financial status provided by the Veterans Health Administration is noteworthy. This permits epidemiologic evaluations while minimizing the effect of disparities in medical care. This, along with the existence of electronic health records within the Veterans Affairs health care system (CPRS), enables detailed

FIGURE. Cumulative risk for developing chronic kidney disease according to fitness categories.
observation of history and alterations in health status. These attributes minimize the likelihood of reverse causality and support the validity of fitness-related health benefits.

The study also has limitations inherent in all prospective follow-up evaluations. In addition, the precise cause of CKD was not ascertained. We have no data on proteinuria before the exercise test. However, we controlled for the presence of diabetes and ACE/angiotensin receptor blocker therapy, which are reasonable surrogates for the presence of proteinuria in this cohort. Fitness levels were based on 1 assessment, and follow-up data on the fitness status of the participants were not available. The onset of chronic diseases, their severity, and duration of therapy were not evaluated. Dietary information was also not available in our records. In addition, because all the subjects in the cohort were referred for exercise testing for a clinical reason, a bias could exist that would limit the generalizability of these findings. A potential selection bias may also be an additional limitation of the study. Specifically, creatinine/eGFR measurements used to ascertain the outcome were obtained for clinical purposes, not research purposes. Thus, older and relatively unhealthy individuals or those with additional comorbidities might have had their eGFRs assessed more often than healthier individuals, increasing the likelihood of identifying incident CKD at a higher rate, independent of the exercise capacity. Finally, our cohort comprised only men and therefore our findings are applicable primarily to men.

**CONCLUSION AND CLINICAL RELEVANCE**

Our findings support an inverse, independent, and graded association between higher exercise capacity and the rate of developing CKD in men. The average exercise capacity of approximately more than 6.5 METs necessary to realize these health benefits is achievable by many middle-aged and older men by daily exercises such as brisk walking. Thus, improved cardiorespiratory fitness may provide a potential intervention for men at risk for CKD development. Future exercise interventional studies are warranted to establish exercise as an effective intervention to prevent or at least attenuate the development of CKD.

**Abbreviations and Acronyms:**
ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CPRS = Computerized Patient Record System; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ICD-9 = International Classification of Diseases, Ninth Revision; MET = metabolic equivalent

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**REFERENCES**