Large epidemiologic studies support that increased cardiorespiratory fitness (CRF) attenuates the development of chronic disease and mortality risk in apparently healthy individuals and in patients with comorbidities.
In general, the risk is highest for pts within the lowest fitness category, with a progressive decline in risk observed as fitness increases regardless of age, sex, or risk factors.
Mortality Risk Within Each Fitness Category for DM2 Individuals with and without Additional Risk Factors

Kokkinos P, Faselis C, Nylen E.
Diabetes Care 2012
Mortality Risk for the Entire Cohort According to Fitness Categories

Kokkinos P., Faselis C, Myers J, et al., Circulation 2014;130: 653-658

If your age is <50 years: Peak MET >8
If your age is ≥50 years: Peak MET >7

* p<0.001
CRF and Incidence of Heart Failure in the Veterans Exercise Testing Study (n=21,080 ; 1,902 events)

Adjusted risk for Major Adverse Coronary Events According Fitness Categories

Conclusions: In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause (14%) and cardiovascular mortality and CVD events, (31%) with greater absolute benefits in patients at greater baseline risk.
There is also evidence that statins may attenuate exercise capacity via unfavorable effects on muscle and mitochondria structure and function.

Question: What is the CRF-Statin association and health impact in patients treated with statins?
10,043 Dyslipidemic patients

Statins: 5,033

No Statins: 5,010

Mean Age: 58.8 ±10.9 years

Median follow-up: 10 years

2,318 patients died - average yearly rate of 22 deaths/1,000 person-years.
Both statins and fitness lowered mortality risk independently.

- Risk reduction for **Statins Only**: 35%
- Risk reduction for **Fitness Only**: 26% - 63%

Mortality Risk According to Fitness Categories
Lancet 2013; 381: 394-99

* p<0.0001

Relative Risk

≤5 METs
5.1-7 METs
7.1-9 METs
>9 METs

Statin Therapy (n=5,032)
No Statin Therapy (n=5,011)
High-Fit (>9 METs)

Low-Fit (5.1-7.0 METs)

Moderate-Fit (7.1-9.0 METs)

Least-Fit (≤5 METs)

Referent

Statins

No Statins

* p<0.0001


Statin/Fitness Interaction and Mortality in Dyslipidemias
Exercise Capacity and Statin vs No Statin Therapy

Myers J, Kokkinos P.


* p<0.04
Mortality Risk According to CRF in Hypertensive, Dyslipidemic Patients Treated and Not Treated with Statins


American Journal of Hypertension; 2014: 422–430
Both CRF and statin therapy lower mortality risk similarly in dyslipidemic patients.

Combined CRF and Statins is more effective than either treatment alone!
Several studies and meta-analyses of randomized controlled trials have reported unfavorable glycemic homeostasis and higher dose-related risk of type 2 diabetes (T2DM) incidence in those treated with statins compared non-statin treated.

In the Diabetes Prevention Program (DPP) this risk is placed at about 30% higher compared to controls.

Statins and DM2 Incidence: Proposed Mechanisms

- L-Type Ca Channel blockage
- ↓ ATP generation
- ↓ GLUT-4
- ↓ Adiponectin
- ↓ Exercise capacity

↓ Insulin secretion

↓ Insulin Sensitivity

Type 2 Diabetes
Lifestyle interventions, including increased physical activity improve metabolic parameters and attenuate the risk of developing T2DM.
Long-term sustainability of DM2 Prevention Approaches: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Haw JS., et al., JAMA Intern Med. 2017;177(12):1808-1817

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Active intervention, y</th>
<th>End of Active Intervention, RR (95% CI)</th>
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<tbody>
<tr>
<td><strong>LSM Trials</strong></td>
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<td></td>
</tr>
<tr>
<td>Swinburn et al, 2001</td>
<td>Reduced-fat diet</td>
<td>1.0</td>
<td>0.76 (0.25-2.34)</td>
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<tr>
<td>DPP, 2002, 2009b</td>
<td>Diet and physical activity</td>
<td>2.8</td>
<td>0.48 (0.41-0.58)</td>
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<tr>
<td>DPS, 2001, 2013</td>
<td>Diet and physical activity</td>
<td>4.0</td>
<td>0.44 (0.29-0.68)</td>
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<tr>
<td>Da Qing, 1997, 2008</td>
<td>Diet and physical activity</td>
<td>6.0</td>
<td>0.68 (0.54-0.85)</td>
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<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td></td>
<td>0.55 (0.43-0.70)</td>
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<tr>
<td><strong>Medication Trials</strong></td>
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</tr>
<tr>
<td>Eriksson et al, 2006</td>
<td>Glipizide</td>
<td>0.5</td>
<td>0.41 (0.01-11.3)</td>
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<td>DREAM, 2006, 2011</td>
<td>Rosiglitazone</td>
<td>3.0</td>
<td>0.43 (0.37-0.48)</td>
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<tr>
<td>DREAM, 2006, 2011b</td>
<td>Ramipril</td>
<td>3.0</td>
<td>0.93 (0.82-1.04)</td>
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<tr>
<td>DPP, 2002, 2003</td>
<td>Metformin</td>
<td>2.8</td>
<td>0.76 (0.66-0.88)</td>
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<tr>
<td>STOP-NIDDM, 2002</td>
<td>Acarbose</td>
<td>3.0</td>
<td>0.78 (0.68-0.90)</td>
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<tr>
<td>ORIGIN, 2012</td>
<td>Insulin glargine</td>
<td>6.2</td>
<td>0.79 (0.67-0.94)</td>
</tr>
<tr>
<td><strong>Pooled estimate</strong></td>
<td></td>
<td></td>
<td>0.71 (0.55-0.92)</td>
</tr>
</tbody>
</table>
Exercise

Statin Therapy

➢ Can improved CRF neutralize the increased risk of DM2 associated with statin therapy?

➢ Thus, we examined the CRF-Statin interaction on the risk of T2DM in statin-treated patients.

DM2 RISK

The statin-related increased risk may be modulated by increased CRF!
Cohort

We identified dyslipidemic patients with a normal exercise tolerance test (ETT) performed during 1986-2014 at the Washington, DC or Palo Alto, CA, VA Medical Centers.

We Excluded those with:

- T2DM prior to ETT or Statin therapy
- Unable to complete the test or had an ischemic response
- Exercise capacity <2 METs
- BMI <18.5 kg/m²
- Impaired chronotropic response to exercise
- Implanted pacemaker
- Developed LBBB during the test
- Chronic obstructive pulmonary disease
- HIV/AIDS
Final Cohort Characteristics

- The final cohort consisted of 4,092 statin-treated patients
- Age = 58.8 ± 10.9 years
- We also identified a non-statin-treated cohort (n=3,001) to serve as controls
- Age = 57.2 ± 11.2 years with no evidence of T2DM prior to the exercise test.

Age-Adjusted Fitness Categories

- We stratified the Statin-Treated cohort into 4 age groups: <50; 50-59; 60-69; and ≥70 yrs.
- We then identified quartiles of peak METs achieved within each age group.
- Finally, we combined the quartiles to form the CRF categories for the entire cohort.

<table>
<thead>
<tr>
<th>CRF Categories</th>
<th>≤ 25%</th>
<th>&gt;25%-50%</th>
<th>&gt;50%-75%</th>
<th>&gt; 75%</th>
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</thead>
<tbody>
<tr>
<td>Least-Fit (n=954)</td>
<td>4.8±1.2</td>
<td>6.5±1.1</td>
<td>8.0±1.1</td>
<td>10.3±2.1</td>
</tr>
<tr>
<td>Low-Fit (n=1,201)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate-Fit (n=1,242)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>High-Fit (n=695)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.2±10.8</td>
<td>58.8±11.0</td>
<td>58.8±10.7</td>
<td>59.5±10.9</td>
</tr>
<tr>
<td>Cohort Characteristics According to CRF Categories</td>
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<td>-----------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.2±110.9</td>
<td>58.8±11.0</td>
<td>58.8 ±10.7</td>
<td>59.5±10.9</td>
</tr>
<tr>
<td>BMI (kg/m²) *</td>
<td>30.3±6.1</td>
<td>29.7±5.0</td>
<td>28.8±4.3</td>
<td>27.6±4.0</td>
</tr>
<tr>
<td>Rest SBP (mm Hg) *</td>
<td>131.9±20.9</td>
<td>129.8±19.6</td>
<td>116.7±18.0</td>
<td>127.0±17.9</td>
</tr>
<tr>
<td>Rest DBP (mm Hg) *</td>
<td>80.3±12.3</td>
<td>78.8±11.5</td>
<td>78.0±10.8</td>
<td>78.1±10.9</td>
</tr>
<tr>
<td>Glucose (mg/dL) *</td>
<td>105.5 ±33</td>
<td>101.4 ±24.6</td>
<td>98.9±21.0</td>
<td>95.0±14.7</td>
</tr>
<tr>
<td>Smoking (%) *</td>
<td>408 (43)</td>
<td>448 (37)</td>
<td>326 (27)</td>
<td>144 (21)</td>
</tr>
<tr>
<td>HTN*</td>
<td>824 (86)</td>
<td>984 (82)</td>
<td>957 (77)</td>
<td>447 (64)</td>
</tr>
<tr>
<td>Medications*</td>
<td>879 (92)</td>
<td>1,089 (91)</td>
<td>1,058 (85)</td>
<td>496 (26)</td>
</tr>
<tr>
<td>Sleep Apnea*</td>
<td>113 (12)</td>
<td>168 (14)</td>
<td>171 (14)</td>
<td>47 (7)</td>
</tr>
<tr>
<td>Alcohol/Drugs*</td>
<td>108 (11)</td>
<td>130 (11)</td>
<td>105 (9)</td>
<td>39 (6)</td>
</tr>
</tbody>
</table>
METHODS – Statistical Analyses

For Cox proportional hazard models we adjusted for the following baseline covariates:

- Age
- BMI
- BP
- Race
- HTN, Smoking, Sleep Apnea, Drug/Alcohol abuse
- Medications for CVD/HTN
Findings

- Mean FU period 8.3 ±5.2 yrs; Median: 8.3 yrs; 35,177 person-years
- 1,075 (26.3%) developed T2DM
- 30.6 T2DM events/1,000 person-yrs of FU
- T2DM incidence was 24% higher in statin-treated patients (HR=1.24; CI:1.11-1.39)
- The CRF-T2DM was inverse, independent and graded. For each 1 MET increase in exercise capacity the adjusted risk of T2DM incidence was 6% lower (HR 0.94; 95% CI, 0.91-0.97; p <0.001).
When CRF were considered, the risk of T2DM decreased progressively as exercise capacity increased.

- **Least-Fit** (4.8±1.2 METs): Relative Risk = 1
- **Low-Fit** (6.5±1.1 METs): Relative Risk = 0.82
- **Mod-Fit** (8.0±1.1 METs): Relative Risk = 0.76
- **High-Fit** (10.3±2.1 METs): Relative Risk = 0.66

* p≤0.001
† p=0.009
Incidence of T2DM According to fitness status in statin-treated patients with dyslipidemia compared to the non-statin treated group

Incidence of T2DM According to fitness status in statin-treated patients with dyslipidemia compared to the non-statin treated group


Adjusted Risk for Type 2 Diabetes

- **Non-Statin treated group**
  - Least-Fit Referent Group: 1
  - Least-Fit: 0.84
  - Most-Fit: 1

- **Statin treated group**
  - Least-Fit: 1.39
  - Most-Fit: 0.93

*P<0.006
Dyslipidemic pts treated with statins had a 24% higher incidence of T2DM compared to those not treated with statins.

When compared to those not treated with statins, the increased incidence of T2DM was only evident in the Least-Fit (39%-50%) and Low-Fit individuals (22%) on statin therapy.
Limitations/Explanations

➢ Fitness was assessed only at baseline.
  ▪ *However, CRF is likely to decrease rather than increase with aging. Thus, the impact of CRF is likely underestimated!*

➢ Onset of comorbidities, their severity, and duration of therapy were not evaluated.

➢ Low-fit individuals are likely to have more comorbidities (i.e. metabolic syndrome), predisposing them to higher risk for DM2.
Despite these limitations, our findings suggest that the statin-induced increased risk of T2DM may be attenuated by moderate improvements in CRF achievable by a brisk walk 30-40 min/day most days of the week (150-200 min/week).

Physical activity is free, relatively low risk with no side-effects.

It complements pharmacologic therapy, likely to lead to lower doses of drug in most cases,
Comparative effectiveness of exercise and drug interventions on mortality outcomes: meta-epidemiological study


➢ Exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of CHD, rehabilitation after stroke, treatment of heart failure, and prevention of DM2.

➢ Exercise interventions should therefore be considered as a viable alternative to, or alongside, drug therapy.
Incidence Rate: 1/259,000

- Significantly Higher during marathon vs half marathon
- Higher in Men vs Women
- Most common cause: Hypertrophic Cardiomyopathy
- Need for a good exam prior to engaging in exercise
No Age-Related Limits!

➢ All evidence supports that even mild forms of exercises confer health benefits independent of age, gender, or chronic conditions!

➢ Exercise adds life to your years and years to your life!
Thank you!