**Official Model Results**

After meeting with Patrick, I realized that I had mis-specified the time to event portion of the survival model. In short, I had time starting at age zero instead of at an individual’s age when they began wearing the accelerometer. After fixing this immortal time bias issue, I found a much stronger association between physical activity volume and incident coronary artery disease than I had previously. Additionally, I was able to run a model with both physical activity volume and physical activity intensity (measured as fraction of physical activity spent at a moderate to vigorous level - % MVPA) and got reasonable results.

Lastly, I checked the performance of the model with physical activity specified as a restricted cubic spline compared to as a restricted quadratic spline and compared to as a linear term. Based on BIC, I concluded that there is no advantage to using a more complex form than a linear model. While this might seem counterintuitive based on previous modeling efforts, I checked and realized that in Dempsey et al., for example, even with a restricted cubic spline the association of physical activity volume and incident CVD was nearly linear. I found the same result for % MVPA and so also model that linearly. Additionally, while a couple of other papers interacted % MVPA and PA volume, I found no significant interaction effects between these two exposures (neither linearly nor comparing as quartiles) and so I simply enter both into a regression together without an interaction term.

This is also now using the sample of individuals of White British ancestry and complete case analysis. These results differ only slightly from those using a pooled ancestry sample or imputed (via MICE) dataset due to the overwhelmingly white sample and the extremely low rates of missingness.

**Table 1: Overview of PA Volume Results for White British Ancestry**

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| --- | --- | --- | --- | --- |
| **Genetic Risk** | **Physical Activity Volume Risk (Lower Risk = MORE Physical Activity)** | | | |
| *20th Percentile* | *40th Percentile* | *60th Percentile* | *80th Percentile* |
| *20th Percentile* | 1 (Reference) | 1.12 (95% CI: 1.08-1.16) | 1.22 (95% CI: 1.14-1.30) | 1.33 (95% CI: 1.21-1.46) |
| *40th Percentile* | 1.26 (95% CI: 1.22-1.30) | 1.41 (95% CI: 1.34-1.48) | 1.53 (95% CI: 1.42-1.65) | 1.68 (95% CI: 1.52-1.85) |
| *60th Percentile* | 1.54 (95% CI: 1.45-1.63) | 1.72 (95% CI: 1.60-1.84) | 1.87 (95% CI: 1.71-2.04) | 2.05 (95% CI: 1.83-2.29) |
| *80th Percentile* | 1.95 (95% CI: 1.77-2.13) | 2.17 (95% CI: 1.97-2.40) | 2.37 (95% CI: 2.11-2.65) | 2.59 (95% CI: 2.27-2.95) |

The relationship between physical activity volume and incident CAD is extremely strong in these results. A person at the 80th percentile of physical activity risk and the 20th percentile of genetic risk faces a 33% greater hazard of incident CAD than their counterpart at the 20th percentile of physical activity risk. The absolute hazard from a lack of physical activity becomes greater at higher genetic risk groups relative to the reference group. While genetic risk still appears to exhibit a stronger association with incident CAD than physical activity volume, PA volume increases hazard by 1/3 to ½ as much as genetic risk does - a much closer association than in the original results. PA volume and genetic risk each have important independent associations with incident CAD, but their combined association is even more powerful. At the 80th percentile of risk for PA volume and genetic risk, an individual is at a 159% greater risk of incident CAD than an individual in the 20th percentile of risk in both categories.

**Table 2: Overview of PA Intensity (% MVPA) Results for White British Ancestry**

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| --- | --- | --- | --- | --- |
| **Genetic Risk** | **% MVPA Risk (Lower Risk = MORE Physical Activity)** | | | |
| *20th Percentile* | *40th Percentile* | *60th Percentile* | *80th Percentile* |
| *20th Percentile* | 1 (Reference) | 1.15 (95% CI: 1.09-1.20) | 1.29 (95% CI: 1.18-1.41) | 1.48 (95% CI: 1.29-1.69) |
| *40th Percentile* | 1.26 (95% CI: 1.22-1.30) | 1.45 (95% CI: 1.37-1.53) | 1.63 (95% CI: 1.48-1.79) | 1.86 (95% CI: 1.62-2.14) |
| *60th Percentile* | 1.54 (95% CI: 1.45-1.63) | 1.77 (95% CI: 1.64-1.91) | 1.99 (95% CI: 1.79-2.21) | 2.27 (95% CI: 1.96-2.63) |
| *80th Percentile* | 1.95 (95% CI: 1.77-2.13) | 2.24 (95% CI: 2.01-2.48) | 2.52 (95% CI: 2.21-2.86) | 2.88 (95% CI: 2.44-3.39) |

In this analysis, PA volume from earlier is kept in the regression as a control variable and the percent of total physical activity from moderate to vigorous physical activity (% MVPA) is treated as the primary physical activity exposure. The results align well with the previous analysis but demonstrate that physical activity intensity has an even stronger association with incident CAD than does physical activity volume alone. Specifically, an individual at the 80th percentile of % MVPA risk and 20th percentile of genetic risk but the same level of physical activity volume has a 48% greater hazard of incident CAD than an individual at the 20th percentile of % MVPA risk. The combined impact of high genetic predisposition to CAD and % MVPA risk is especially troubling, as an individual at the 80th percentile of both categories faces a 188% greater hazard of incident CAD than an individual at the 20th percentile.

In the following section, I reproduce the above tables as figures for both PA volume and intensity. I thought stratifying on genetic risk might be more interesting than stratifying on PA (as I had done earlier) but I’m very open to suggestions regarding how best to present these figures.

**Figure 1: Forest Plot of Genetic and Overall PA Volume and Risk of Incident CAD**

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| --- |
| ***20th Percentile of Genetic Risk vs 40th Genetic Risk*** |
| ***20th Percentile of Genetic Risk vs 60th Percentile of Genetic Risk*** |
| ***20th Percentile of Genetic Risk vs 80th Percentile of Genetic Risk*** |
|  |

**% MVPA FIGURE:**

**Figure 2: Forest Plot of Genetic and % MVPA and Risk of Incident CAD**

|  |
| --- |
| ***20th Percentile of Genetic Risk vs 40th Genetic Risk*** |
| ***20th Percentile of Genetic Risk vs 60th Percentile of Genetic Risk*** |
| ***20th Percentile of Genetic Risk vs 80th Percentile of Genetic Risk*** |
|  |