*Results of Dempsey et al., Replication of Overall Physical Activity Results*

From: *“Physical activity volume, intensity, and incident cardiovascular disease”*

**Notes before analysis:**

1. We are NOT using the same outcome as in Dempsey. We use coronary artery disease, whereas they use CVD more broadly.
2. We are using a similar but NOT identical population. Genetic screening means we’re working with around 70k individuals as opposed to 96k in Dempsey. There do not seem to be significant power issues based on this.
3. As a result of these two facts, I wouldn’t necessarily expect us to get estimates that are really close to those in Dempsey et al. However, the fact they generally align well and our estimates are in line with the rest of the literature gives me confidence.
4. I am also using COMPLETE CASE ANALYSIS, whereas Dempsey et al., uses imputation. This results in about 2,000 fewer observations here and should not have a massive impact on results.
5. This is ONLY for OVERALL PHYSICAL ACTIVITY. I will be repeating this replication using PA intensity (MVPA).

**Dempsey et al. analytical approach:**

***The Model***

Restricted cubic spline model with three evenly spaced knots and age as the underlying time scale. We both use physical activity energy expenditure as the primary exposure (a validated measure of overall physical activity). We followed the same process, although I also conducted the analyses with 4 knots and as a restricted quadratic spline and found the results were not very sensitive to this functional form change.

Dempsey stratifies by variables that violate the proportional hazards assumption. I did this for the confounders that violated the proportional hazards assumption (biological sex, education, employment status, smoking status) and found it does not change the coefficient on the exposure much at all.

**HOWEVER,**

\*\*\*\* I find that the proportional hazards assumption IS violated for physical activity energy expenditure. As a result, I will present results both without adjusting for this and age-adjusted. The primary difference here is that the association becomes much weaker for an individual aged 65 and much stronger for an individual aged 75 (ages chosen because of apparent nonlinearity across these ages).

***Covariates in the Two Models***

Model 0: Control for sex and season of wear

Model 1: Adding education level, employment status, Townsend index, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of heart disease, BP meds, cholesterol meds, mobility problems, prevalent cancer, parental history of cancer, insulin medication/diabetes, ethnicity, we added polygenic score and genetic principal components just to make sure these don’t significantly change things.

We got these values the same way as in Dempsey and most other accelerometer-based analyses in the UK Biobank. We took the most recently available value of the covariate BEFORE accelerometer wear time started for time-varying covariates measured at multiple time points.

**Table 1: Covariate Comparison between our study and Dempsey (highlighted in red above means we excluded)**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Coding in Dempsey** | **Coding in this analysis** |
| Education Level | A bit vague but appears to separate as no degree, university degree, other | Followed same process |
| Smoking Status | Kept as factor variable with never, previous, current | Followed same process |
| Alcohol Intake | Measured as Never/Rarely, Less than twice a week, Usually/Often | Followed same process (ambiguity on never/rarely but took as special occasions or less) |
| Salt Intake | Kept as never, sometimes, usually/always with meals | Followed same process |
| Oily Fish Consumption | Coded as more than once a week or not | Followed same process |
| Fruit & Vegetable Consumption | Coded as a score from 0-4 taking into account dried/fresh fruit consumption and raw/cooked vegetable consumption in 24-hour period | This was a strange one. I added them up and then split the variable into quartiles to simulate this process, which yielded similar results |
| Red/Processed Meat Consumption | Weekly frequency of red/processed meat consumption | Followed same process |
| Average Sleep Duration | Continuous variable based on average given by individual | Followed same process |
| Parental History of Heart Disease/Cancer | Dichotomous variable based on if either mother or father had history of heart disease or cancer | This one didn’t make much sense to me. I coded instead as a dichotomous variable based on whether mother or father had history of heart disease only |
| Medication Use | Coded as whether person has cholesterol or blood pressure medication | Followed same process |
| Mobility Problems | Coded as 1 if person indicated any difficulty (from slight to major) and 0 otherwise | Followed same process |
| Employment Status | Coded as 1 if in paid employment or self-employed and 0 otherwise | Followed same process |

There are some differences in how we coded variables and what variables we include in the analysis but I see little reason *a priori* to expect any of this to have a strong influence on our comparison of results.

**Summary of Covariates**

FOR SAKE OF SPACE, I HAVE ATTACHED THIS AS SEPARATE WORD DOCUMENT. The main point here is that our covariates look relatively similar to Dempsey et al. This is available in “Dempsey Rep Summary Stats.docx”

**Proportional Hazards Test**

Chart, scatter chart

Description automatically generated

This graph shows why we must use age-specific hazards for this analysis. There is a strong nonlinearity, particularly between about 65 and 70 (which is why the comparison groups are 65 and 75 in this analysis).

**How does Dempsey et al. present their results?**

Dempsey et al. compare a PAEE of 15 to 20, 30, 40, 50, and 60. For context, a PAEE of 15 is *very* low (around the 10th percentile of physical activity), while a PAEE of 60 is close to the 90th percentile. We follow the same process.

**Results Comparison for Model 1 (BOTH age-specific and not age-specific):**

Table 2: Model 1 Comparison Results (NO age-specific estimation)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PAEE (kJ/kg/day)** | **15** | **20** | **30** | **40** | **50** | **60** |
| Dempsey Model 1 | 1 (Reference) | 0.88  (95% CI: 0.80-0.96) | 0.73  (95% CI: 0.60-0.88) | 0.69  (95% CI: 0.58-0.82) | 0.64  (95% CI: 0.53-0.76) | 0.60  (95% CI: 0.49-0.73) |
| Our Model 1 | 1 (Reference) | 0.96  (95% CI: 0.92-1.00) | 0.89  (95% CI: 0.77-1.01) | 0.81  (95% CI: 0.63-1.06) | 0.78  (95% CI: 0.65-0.95) | 0.76  (95% CI: 0.62-0.95) |
| Our Model 1  (Age 65) | 1 (Reference) | 0.97  (95% CI: 0.92-1.04) | 0.93  (95% CI: 0.77-1.12) | 0.89  (95% CI: 0.71-1.11) | 0.86  (95% CI: 0.69-1.07) | 0.83  (95% CI: 0.63-1.09) |
| Our Model 1  (Age 75) | 1 (Reference) | 0.94  (95% CI: 0.89-1.00) | 0.84  (95% CI: 0.70-1.00) | 0.75  (95% CI: 0.61-0.92) | 0.68  (95% CI: 0.54-0.85) | 0.62  (95% CI: 0.45-0.84) |

These results show that the association between CAD and PAEE we found is generally somewhat weaker than that found between CVD and PAEE by Dempsey et al. This also does not appear to be an artifact of lower statistical power, as our confidence intervals are only marginally wider than theirs.

**How does this compare to the rest of the literature?**

There aren’t many studies that exist comparing objectively measured physical activity with CAD. However, in the literature I have reviewed, our estimates appear to be largely in line with those using subjective physical activity.

Most relevant is likely “Associations of Fitness, Physical Activity, Strength, and Genetic Risk with Cardiovascular Disease,” which used subjective PA for 502,000 individuals in the UK Biobank and found an HR of 0.95 per change in PA for incident CHD. A standard deviation of PAEE is a bit over 11 in our case, so this lines up well with what we would expect (stronger effect in objective PA). However, when we stratify by age we see a MUCH stronger association at age 75 than either overall or at age 65. This all aligns fairly well with what I had expected in advance.