Physical activity is associated with reduced risk of liver disease in the prospective UK Biobank cohort

Carolin V. Schneider, Inuk Zandvakili, Christoph A. Thaiss, Kai Markus Schneider

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Fig. S1: Association between physical activity and risk of liver disease. Physical activity measured by accelerometer was grouped into ventiles (1 lowest activity – 20 highest activity). Relative risk for the association between physical activity and risk of A) overall liver disease (K70-77+C22+B18), B) NAFLD K76.0) plotted against the mean physical activity value within each quartile of no-wear-time adjusted accelerometer average. Solid lines show linear regression of HRs versus quartile mean; adjusted for age, sex, BMI and alcohol consumption. Normality was tested using the Kolmogorov Smirnov test and all variables were found to be normally distributed and homoscedasticity was tested using the Goldfeld-Quandt test. All requirements for linear regression were met. A) $R^2=0.81$ and B) $R^2=0.79$. 
Fig. S2: Linear Spearman Correlation of Acceleration average with proton density fat fraction of the liver in participants without preknown liver disease.
Fig. S3: Prospective liver-disease risk as a function of physical activity in subgroups that are at risk of developing liver disease. (A) Risk of overall liver disease as a function of physical activity in overweight participants. Participants were followed prospectively from the time of wearing the accelerometer until death or end of follow-up. (B) Risk of overall liver disease as a function of physical activity in elderly participants (age > 60 years). C) Risk of overall liver disease as a function of physical activity in participants with current alcohol consumption. Hazard ratios were calculated by Cox regression, adjusted for sex, age, BMI and alcohol consumption. The p-values given in the figure are overall p-values comparing all four groups.
A) Obese: Quartile 4 vs.1: HR: 0.38[0.16-0.88], B) Elderly: Quartile 4 vs.1: HR: 0.39[0.26-0.58], Quartile 3 vs.1: HR: 0.57[0.42-0.78]; Quartile 2 vs.1: HR: 0.73[0.55-0.96]; C) Current alcohol drinker: Quartile 4 vs.1: HR: 0.39[0.26-0.56]; Quartile 3 vs.1: HR: 0.61[0.45-0.83]; Quartile 2 vs.1: HR: 0.75[0.58-0.98].
Table S1. Cox regression models for liver disease and NAFLD in most physically active quartile of participants (quartile 4) vs. the least physical active (quartile 1).  

| Risk of overall liver disease | Risk of NAFLD |
|------------------------------|---------------|
|                              |   Hazard ratio (HR) | P value |    Hazard ratio (HR) | P value |
| Unadjusted                   |   0.26 [0.19-0.37] | <.0001  |   0.25 [0.14-0.44] | <.0001  |
| Adjusted for BMI, age, sex and alcohol consumption |   0.41 [0.29-0.59] | <.0001  |   0.39 [0.21-0.70] | <.0001  |
| Adjusted for BMI, age, sex, alcohol consumption and month of accelerometry |   0.41 [0.30-0.61] | <.0001  |   0.40 [0.22-0.74] | .003    |
| Adjusted for smoking, BMI, age and alcohol consumption |   0.42 [0.29-0.60] | <.0001  |   0.39 [0.21-0.71] | .002    |
| Adjusted for BMI, age, sex, alcohol consumption, hypertension, hyperlipidemia, waist circumference and DM |   0.49 [0.34-0.71] | <.0001  |   0.47 [0.31-0.73] | .003    |
| Adjusted for overall health index, sleep duration, age, sex, alcohol consumption and BMI |   0.47 [0.31-0.67] | <.0001  |   0.45 [0.25-0.85] | .010    |
| Adjusted for age, sex, BMI, alcohol consumption, overall accelerometer wear-time, overall health index and number of falls in previous year |   0.47 [0.33-0.67] | <.0001  |   0.46 [0.35-0.84] | .012    |
| Adjusted for age, sex, BMI, alcohol consumption, DM, mean kcal intake, mean sugar intake, mean fat intake and mean carbohydrate intake |   0.40 [0.28-0.61] | <.0001  |   0.36 [0.18-0.73] | .005    |
| Adjusted for all above       |   0.51 [0.33-0.78] | .0001   |   0.47 [0.28-0.77] | .017    |

‘Unadjusted’ represents the comparison between quartile 1 and 4 without accounting for the mentioned cofactors in Table 1. More information on any of the cofactors is given in Table 1. Abbreviations: CI, confidence interval; BMI, body mass index; DM, diabetes mellitus.
Table S2: Number of participants diagnosed with liver diseases in the subgroup of participants with liver diseases prior to accelerometry.

| ICD10 code                                      | Number of participants |
|------------------------------------------------|------------------------|
| Alcoholic liver disease (K70)                   | 59                     |
| Toxic liver disease (K71)                       | 8                      |
| Hepatic failure (K72)                           | 25                     |
| Chronic hepatitis (K73)                         | 21                     |
| Fibrosis and cirrhosis (K74)                    | 93                     |
| Primary biliary cirrhosis (K743)                | 27                     |
| Other and unspecified cirrhosis of liver (K746) | 49                     |
| Other inflammatory liver diseases (K75)         | 90                     |
| Granulomatous hepatitis (K753)                  | 5                      |
| Autoimmune hepatitis (K754)                     | 18                     |
| Nonalcoholic steatohepatitis (K758)             | 17                     |
| Inflammatory liver disease, unspecified (K759)  | 32                     |
| Other diseases of liver (K76)                   | 480                    |
| Fatty liver disease (K760)                      | 246                    |
| Chronic passive congestion of liver (K761)      | 2                      |
| Peliosis hepatis (K764)                         | 1                      |
| Portal hypertension (K766)                      | 44                     |
| Hepatorenal syndrome (K767)                     | 2                      |
| Other specified diseases of liver (K768)        | 148                    |
| Liver disease, unspecified (K769)               | 75                     |
| Liver disorders in diseases classified elsewhere (K77) | 2                   |
| Malignant neoplasm of liver and intrahepatic bile ducts (C22) | 12                   |
| Liver cell carcinoma (C220)                     | 5                      |
| Chronic viral hepatitis (B18)                   | 65                     |
| Primary sclerosing cholangitis (K830)           | 14                     |
| Hemochromatosis (E831)                          | 9                      |

Multiple ICD10 codes per participant are possible.
Table S3: Descriptive characteristics of the samples by accelerometer average quartiles in participants with prior liver disease.

| Accelerometer: Acceleration average in participants with previously known liver disease | Quartile 1, n = 178 | Quartile 2, n = 179 | Quartile 3, n = 179 | Quartile 4, n = 178 |
|----------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Acceleration (mgravity), mean (SD)     | 15 (3)               | 21 (1)               | 27 (2)               | 37 (16)              |
| Days of accelerometer wearing (days), mean (SD) | 7(1)                | 7(1)                | 7(1)                | 7(1)                |
| Month of accelerometry, mean (SD)      | 7 (3)                | 7 (3)                | 7 (3)                | 7 (3)                |
| Deaths, no. (%)                        | 28 (16)              | 10 (6)               | 8 (5)                | 4 (2)                |
| Death caused by liver diseases, no. (%) | 9 (5.1)              | 3 (1.7)              | 2 (1.1)              | 1 (0.6)              |
| Death secondary caused by liver diseases, no. (%) | 8 (4.5)              | 3 (1.7)              | 1 (0.6)              | 1 (0.6)              |
| Survival (years), mean (SD)            | 5.0 (1.3)            | 5.4 (1.0)            | 5.5 (0.8)            | 5.6 (0.7)            |
| Progression of liver diseases during follow up |                      |                      |                      |                      |
| Overall liver disease progression, no. (%) | 17 (10)             | 11 (6)               | 11 (6)               | 9 (5)                |
| Fibrosis/Cirrhosis, no. (%)            | 9 (5)                | 5 (3)                | 3 (2)                | 2 (1)                |
| Hepatic failure, no. (%)               | 4 (2)                | 1 (1)                | 0 (0)                | 1 (1)                |
| Malignant liver diseases, no. (%)      | 4 (2)                | 0 (0)                | 1 (1)                | 0 (0)                |
| Varices                                | 18                   | 16                   | 7                    | 6                    |
| Ascites                                | 15                   | 13                   | 5                    | 4                    |
| Portal Hypertension                    | 6                    | 3                    | 2                    | 1                    |
| Characteristics                        |                      |                      |                      |                      |
| Age at accelerometry (years), mean     | 64.7 (6.8)           | 63.3 (7.5)           | 62.1 (7.7)           | 61.3 (7.4)           |
| Female sex, no. (%)                    | 75 (42.1)            | 95 (53.1)            | 96 (53.6)            | 101 (56.7)           |
| White ethnicity, no. (%)               | 172 (96.6)           | 172 (96.1)           | 171 (95.5)           | 173 (97.1)           |
| Missing, no. (%)                       | 0 (0)                | 0 (0)                | 0 (0)                | 0 (0)                |
| Smoking, no. (%)                       |                      |                      |                      |                      |
| Never, no. (%)                         | 79 (44.4)            | 79 (44.1)            | 93 (52.0)            | 82 (46.1)            |
| Previous, no. (%)                      | 74 (41.6)            | 77 (43.1)            | 68 (38.0)            | 76 (62.7)            |
| Current, no. (%)                       | 25 (14.0)            | 23 (12.8)            | 17 (9.4)             | 19 (10.6)            |
| Missing, no. (%)                       | 0 (0)                | 0 (0)                | 1 (0.6)              | 1 (0.6)              |
| Accelerometer: Acceleration average in participants with previously known liver disease | Quartile 1, \( n = 178 \) | Quartile 2, \( n = 179 \) | Quartile 3, \( n = 179 \) | Quartile 4, \( n = 178 \) |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Alcohol intake (g/d) mean (SD)                | 9.0 (14.1)      | 7.2 (10.8)      | 8.6 (11.7)      | 7.9 (11.3)      |
| Alcohol consumption, no. (%)                  |                 |                 |                 |                 |
| Never, no. (%)                                | 7 (3.9)         | 5 (2.8)         | 8 (4.4)         | 9 (5.1)         |
| Previous drinker, no. (%)                    | 15 (8.4)        | 21 (11.7)       | 13 (7.3)        | 12 (6.7)        |
| Current drinker, no. (%)                     | 155 (87.1)      | 153 (85.5)      | 158 (88.3)      | 157 (88.2)      |
| Missing, no. (%)                              | 1 (0.6)         | 0 (0.0)         | 0 (0.0)         | 0 (0.0)         |
| Nutrition                                     |                 |                 |                 |                 |
| Sleep (h), mean (SD)                          | 7(1)            | 7(1)            | 7(1)            | 7(1)            |
| Missing, no. (%)                              | 0 (0)           | 0 (0)           | 1 (1)           | 0 (0)           |
| BMI, mean (SD)                                | 30.1 (6.0)      | 29.9 (5.5)      | 29.1 (5.6)      | 27.1 (4.8)      |
| Obese ≥30 kg m\(^{-2}\), no. (%)             | 91 (51)         | 89 (50)         | 82 (46)         | 49 (28)         |
| Missing, no. (%)                              | 3 (2)           | 1 (1)           | 0 (0)           | 2 (1)           |
| Diagnosis of diabetes, no. (%)                | 29 (16.3)       | 29 (16.2)       | 15 (8.4)        | 8 (4.5)         |
| Missing, no. (%)                              | 0 (0)           | 0 (0)           | 0 (0)           | 0 (0)           |
| Waist circumference (cm), mean (SD)           | 100 (15)        | 96 (13)         | 95 (14)         | 89 (14)         |
| Missing, no. (%)                              | 1 (0)           | 1 (0)           | 0 (0)           | 0 (0)           |
| Dyslipidemia, no. (%)                         | 67 (38)         | 51 (29)         | 46 (26)         | 26 (14)         |
| Missing, no. (%)                              | 0 (0)           | 0 (0)           | 0 (0)           | 0 (0)           |
| Hypertension, no (%)                          | 105 (59)        | 86 (48)         | 79 (44)         | 58 (33)         |
| Missing, no. (%)                              | 0 (0)           | 0 (0)           | 0 (0)           | 0 (0)           |
| Number of Falls, no. (SD)                    | 1.3 (0.4)       | 1.4 (0.7)       | 1.4 (0.7)       | 1.4 (0.6)       |
| Missing, no. (%)                              | 2 (1)           | 0 (0)           | 1 (1)           | 0 (0)           |
| Overall health rating, no. (%)                | 2.8 (0.8)       | 2.6 (0.8)       | 2.3 (0.8)       | 2.2 (0.8)       |
| Missing, no. (%)                              | 0 (0)           | 0 (0)           | 1 (1)           | 0 (0)           |
Table S4: Contribution of physical activity, BMI and the interaction term of physical activity and BMI on liver disease development in participants without prior liver disease, adjusted for age, sex and alcohol consumption.

| Cox proportional Hazard model of liver disease development | P value |
|----------------------------------------------------------|---------|
| Physical activity (mg)                                   | .007    |
| BMI (kg/m2)                                              | .013    |
| Physical activity x BMI (kg*mg/m2)                       | .32     |
| Age (years)                                              | .008    |
| Sex                                                      | .093    |
| Alcohol intake (g/d)                                     | .13     |
Table S5: Contribution of physical activity, fat mass of trunk and their interaction term on liver disease development in participants without prior liver disease, adjusted for age, sex and alcohol consumption.

Cox proportional Hazard model of liver disease development

|                                | P value |
|--------------------------------|---------|
| Physical activity (mg)         | <.0001  |
| Fat mass of trunk (kg)         | .049    |
| Physical activity x fat mass of trunk (kg*mg) | .14     |
| Age (years)                    | .015    |
| Sex                            | .043    |
| Alcohol intake (g/d)           | .31     |
Table S6: Estimated minutes of activity equaling the accelerometer average/h per quartile group for a fictive 80kg male participant with liver disease.

| Activity                                      | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|-----------------------------------------------|------------|------------|------------|------------|
| Accelerometer average                         | 15/h       | 21/h       | 27/h       | 37/h       |
| Acceleration estimation of 17h/day equals     | 255/d      | 357/d      | 459/d      | 629/d      |
| Estimated number of steps/day                 | 4500       | 6750       | 8250       | 11500      |
| Minutes of very slow walking (1.5 km/h)       | 168        | 235        | 302        | 415        |
| Minutes of walking (4 km/h)                   | 70         | 97         | 125        | 172        |
| Minutes of fast running (10km/h)              | 15         | 21         | 28         | 38         |
| Minutes of slow cycling (10km/h)              | 37         | 52         | 67         | 91         |

For estimated minutes activity the acceleration average per hour was multiplied with the estimated waking hours (24h-7h sleeping). Acceleration was then converted to MET (Metabolic equivalent of task). The following estimations were calculated based on previous work(38,39); Very slow walking=3 METs=91mg; Walking=4.5METs=220mg; fast running=11METs=1000mg; Cycling=6MET=414mg; ~1000steps per kilometer of walking was estimated for number of steps/day.

Example: A fictive 80kg male participant with current physical activity in Quartile 1, can increase his activity by walking 40 minutes more per day to reach Quartile 2 and may decrease his risk of liver disease by these measures.