**Additional File 6**

Linear mixed model of fatigue (FSS-9) adjusted for sociodemographic and clinical factors among patients receiving methadone as OAT opioid (N = 209)

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| --- | --- |
|  | Fixed effects |
|  | Effect estimate |  | Time trend (per year) |
|  | Estimate (95 % CI) | p-value |  | Slope (95 % CI) | p-value |
| FSS-9 sum score | 48 (17 – 79) | 0.003 |  | 29.0 (-8.6 – 66.5) | 0.129 |
| Female | *7.3 (2.5 – 12.2)*  | *0.003* |  | -2.8 (-8.9 – 3.2) | 0.358 |
| Age per 10 years1) | -0.3 (-2.6 – 1.9) | 0.784 |  | 1.1 (-1.9 – 4.0) | 0.486 |
| Educational level | -1.7 (-4.3 – 1.0) | 0.220 |  | 1.7 (-1.6 – 5.1) | 0.304 |
| Unstable housing situation | 1.3 (-6.6 – 9.1) | 0.752 |  | -1.1 (-11.6 – 9.5) | 0.844 |
| OAT opioid ratio | -0.4 (-7.7 – 6.9) | 0.909 |  | -0.3 (-11.9 – 11.3) | 0.958 |
| Debt difficulties | *4.9 (0.7 – 9.1)* | *0.023* |  | -0.4 (-5.9 – 5.1) | 0.885 |
| Injecting substance use | -0.2 (-5.1 – 4.6) | 0.922 |  | -0.9 (-6.8 – 4.9) | 0.751 |
| *Frequent use of substances*  |
| Benzodiazepines  | *6.0 (1.6 – 10.5)* | *0.008* |  | *-6.8 (-12.5 – -1.1)* | *0.020* |
| Alcohol | -0.8 (-6.0 – 4.3) | 0.747 |  | 4.4 (-3.1 – 11.9) | 0.247 |
| Cannabis | 1.9 (-2.5 – 6.3) | 0.393 |  | 3.0 (-2.7 – 8.6) | 0.300 |
| Opioids | 0.4 (-8.3 – 9.0) | 0.934 |  | -1.2 (-13.9 – 11.6) | 0.858 |
| Stimulants2) | -2.6 (-8.6 – 3.3) | 0.388 |  | 2.8 (-4.6 – 10.2) | 0.451 |
| *Chronic infectious diseases* |
| Hepatitis B virus infection | 17.4 (-11.5 – 46.2) | 0.458 |  | -10.6 (-26.2 – 4.9) | 0.179 |
| Hepatitis C virus infection* Detected

 - High. vs. low viral load | -12.5 (-33.8 – 8.8)*31.5 (1.5 – 61.5)*  | 0.249*0.040* |  | -*-44.6 (-81.7 – -7.5)* | -*0.019* |
| HIV | 10.7 (-8.4 – 29.8) | 0.272 |  | 4.6 (-20.2 – 29.4) | 0.716 |
| *Liver stiffness* |
| Transient elastography per 10 kPa | 3.3 (-1.4 – 8.1) | 0.167 |  | -*6.2 (-11.7 – -0.7)* | *0.027* |
| APRI score per 1 unit | -1.0 (-3.3 – 1.3) | 0.397 |  | 1.6 (-1.0 – 4.1) | 0.235 |
| *Hematologic and biochemical blood samples (continuous variables)* |
| Hemoglobin per 1 unit (g/dL) | -0.5 (-1.9 – 0.9) | 0.458 |  | -0.5 (-2.3 – 1.3) | 0.558 |
| eGFR per 30 units (ml/min/1.73m2) | -0.9 (-3.2 – 1.3) | 0.414 |  | 0.0 (-1.1 – 4.2) | 0.463 |
| CRP per 10 units (ml/L) | -0.2 (-1.3 – 1.0) | 0.759 |  | 0.2 (-1.2 – 2.4) | 0.834 |