Lifestyle factors during acute Epstein-Barr virus infection in adolescents predicts' physical activity six months later.

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Short running title
Physical activity following Epstein-Barr virus infection

Abstract

Aim: Acute Epstein-Barr virus (EBV) infection is a trigger of prolonged fatigue. This study investigated baseline predictors of physical activity six months after an acute EBV infection.

Methods: A total of 200 adolescents (12-20 years old) with acute EBV infection were assessed for 149 possible baseline predictors and followed prospectively. We performed linear regression analysis to assess possible associations between baseline predictors and steps per day at six months.

Results: In the final multiple linear regression model, physical activity six months after acute EBV infection was significantly and independently predicted by baseline physical activity (steps per day), substance use (alcohol and illicit drugs), and human growth hormone (adjusted R^2=0.20).

Conclusion: Physical activity six months after acute EBV infection is to a larger extent predicted by baseline variables related to lifestyle factors than to baseline variables reflecting infectious and immune processes. Physical activity during acute EBV infection seems to facilitate physical activity six months later.

Key Notes

- Lifestyle factors are the main predictors for physical activity six months following acute Epstei-Barr virus (EBV) infection.
- The intensity or quality of infectious- and immune processes does not seem to predict.

- Physical activity during acute EBV-infection seems to facilitate physical activity six months later.

Keywords: Physical activity, Epstein-Barr virus infection, adolescents, chronic fatigue

Background

Epstein-Barr virus (EBV) is a common human pathogen causing a replicative infection in the oropharynx as well as a life-long latent infection of B cells (1). In children, a primary EBV infection normally elicits few, if any, symptoms. In adolescence, however, up to 75 % of infected individuals develops infectious mononucleosis (IM) characterized by fever, pharyngitis, swollen lymph nodes and malaise (2-4). In the adult population, more than 90 % have undergone an EBV infection.

IM is often complicated by prolonged fatigue, and as many as 12-13% of EBV-infected individuals fulfill case definition of chronic fatigue syndrome (CFS) six months after the acute infection (5, 6). Predictors of chronic fatigue development include female sex, previous negative life events, symptom intensity and C-reactive protein (CRP) level during the initial stages of EBV infection (7-11). However, in a recent study, virus load and other infectious markers had no predictive power(11).

Earlier studies suggest that CFS patients have lower activity levels compared to healthy controls (12-14). Graded exercise is an integrated part of some therapy protocols for CFS(15),and physical activity may modulate illness experiences (16, 17) and increase general well-being (17, 18). Furthermore, physical activity impacts markedly on immune processes and might influence underlying disease processes involving the immune system (19, 20).Accordingly, physical activity monitoring has been used as primary endpoint in CFS clinical trials (14).

Still, the relationship between physical activity and chronic fatigue remains to be fully characterized. In particular, predictors of reduced activity level after acute EBV infection has - to the best of our knowledge - never been investigated. Identification of such predictors might inform prophylactic measures as well as rehabilitation programs, and also yield insight into the underlying mechanisms of disability development in post-infectious chronic fatigue and CFS.

Thus, the aim of the present study was to investigate predictors of physical activity six months after acute EBV infection in adolescents. We hypothesized that factors related to symptoms and function, and not infection and immune response, will be the main predictors for physical activity, similar to previously identified predictors of fatigue in the same cohort.

Materials and methods

Study design

This study is a part of the CEBA-project (Chronic Fatigue following acute Epstein-Barr virus Infection in Adolescents; ClinicalTrial ID: NCT02335437), embracing a prospective, cross-sectional and randomized controlled design with a total follow-up time of 21 months. A detailed description has been provided elsewhere(11). Here, only prospective results from the first six months are reported. The project has been approved by the Norwegian National Committee for Ethics in Medical research. All participants provided written informed consent before inclusion.

Participants with EBV infection

Inclusion of participants lasted from March 2015 until November 2016. During this period, EBV infected individuals fulfilling the following criteria were assessed for eligibility(11): a) A serological pattern indicating acute EBV infection (Table 1); b) Age between 12 and 20 years; and c) Living in one of the Norwegian counties Oslo, Akershus or Buskerud. Exclusion criteria were a) More than 6 weeks since debut of symptoms suggesting acute EBV infection; b) Any chronic disease that needed regular use of medication; and c) Pregnancy.

Investigational program

Participants were summoned to a one-day investigational program at the CEBA study center, Akershus University Hospital, Norway. Encounters were scheduled as soon as possible after debut of symptoms (baseline), with a follow-up visit 6 months later. All participants met at 8 a.m. after fasting overnight. They brought morning spot urine in a sterile container, and were instructed to apply a local anesthetic ointment (EMLA®, AstraZeneca) on both antecubital areas one hour before arriving.

The investigational program was carried out in a fixed sequence for all participants by two researchers only (MP and TTA), and included a clinical examination, ultrasound of the spleen, blood and throat swab sampling, autonomic cardiovascular control assessment, pressure pain threshold assessment, cognitive testing and questionnaire charting(11). Blood samples were obtained in a fixed sequence from antecubital venous puncture and assayed for neuroendocrinological, immunological, microbiological, and routine clinical markers. Autonomic testing encompassed continuous, non-invasive recordings of blood pressure, heart rate and stroke volume during 1) supine rest, 2) supine rest with controlled breathing, and 3) upright standing featuring the Task Force Monitor (Model 3040i, CNSystems Medizintechnik, Graz, Austria). Pressure pain threshold was assessed by gradually applying increasing pressure to six predefined areas, using the Commander™ Algometer (JTECH Medical, Midvale, USA). Cognitive test included assessment of working memory, processing speed, cognitive inhibition and flexibility, learning, and memory. The questionnaire included validated inventories of fatigue and CFS, pain, sleep problems, anxiety and depression, worrying, emotional awareness, illness perceptions, perfectionism, life events, quality of life, and functional disabilities. In addition, we included questions regarding clinical symptoms of EBV infection, symptoms pertaining to different case definition of CFS (21, 22), and demographic and lifestyle background variables.

Activity monitoring

Activity monitoring was initiated immediately after the in-hospital investigational program. All participants wore the activPAL^{TM} accelerometer device (PAL Technologies, Glasgow, Scotland) for seven consecutive days. The activPAL^{TM} was attached on the anterior midline on the participants thigh with costum made, waterproof adhesive tape. The participants were instructed to wear the activPAL^{TM} at all times, and only take it off when the recording period was finished. The activPAL^{TM} provides reliable data on both steps and position (23, 24), and is validated for adolescents (25).

Data from the recording units was transferred to a computer running producer developed software. For each participant, all recording epochs were carefully and independently reviewed by two of the authors (MP and TTA). Alternating periods of active and sedentary behavior were required each day; if one recording day was considered to contain erroneous or incomplete data, that entire day was removed from further calculation (Table 2). Doubtful cases were discussed until consensus was reached.

Statistical analysis

All statistical analyses were performed with SPSS statistical software (IBM SPSS Statistic 22 Inc., Chicago, IL, USA). Average steps per day at six months follow-up was predefined as the dependent variable (26). It was estimated that a total of 200 EBV infected individuals would give a power of at least 80 % to detect a predictor variable that explains 5% of the variance in steps per day at six months. Correspondingly, when assessing associations with a binary predictor at a 5% significance level, a total of 200 patients would give a power of 80% to detect a mean difference of 0.4 SD between the two categories. Thus, the study had sufficient power to detect small to medium effect sizes.

The primary analyses featured simple linear regression between steps per day and a total of 149 possible baseline predictors (11). The first screening was performed without imputation and assumptions were checked by visual inspection of residual plots. Thereafter, variables with p-value below 0.1 in the sceening analyses and thus candidates for inclusion in the multiple linear model, were subjected to multiple imputation to replace missing values, creating a total of five complete datasets. All six datasets (five imputed in addition to the original dataset) were included in multiple linear regression modelling assessing each variable's p-value and the effect on the dependent variable's variance (adjusted R^2). In the final models, a p-value < 0.05 was considered statistically significant. To check the stability of the model, all candidate variables were reentered one-by-one in the final model. A wide as well as a strict model were constructed: The wide model consists of all variables that ended up in the final model for one of the six datasets. The strict model was constructed on pooled data from the five imputed datasets. A more detailed explanation of a similar model construction is reported elsewhere (11).

+ sensitivitetsanalyse med bare complete cases? (kun final model)

Results

A total of 895 adolescents with a serological pattern suggesting acute EBV infection were assessed for eligibility, and a total of 200 were included, of which 195 (97.5 %) attended the follow-up visit at six months (Table 3). Serological analyses confirmed acute EBV infections in all included participants.

In simple linear regression analyses, baseline variables of clinical symptoms and functional abilities were most strongly associated with physical activity at six months (Table S1). In addition, baseline emotions, alcohol and narcotics consumption and supine heart rate had some

predictive power, whereas few associations were found to markers of infection, immunity and neuroendocrinology.

In the final multiple linear regression model, baseline steps/day and narcotics consumption were positively and independently associated with steps/day at 6 months, whereas baseline alcohol consumption and serum growth hormone levels were negatively associated (Table 4). Applying a less strict procedure for variable selection, baseline sleepiness, emotional awareness, serum IgG level and supine heart rate added some explanatory power to the model (Table S2). Analyses stratified by sex revealed a higher explanatory power of the models for the females compared to the males. Baseline steps/day remained a statistically significant predictor among females only, whereas baseline alcohol and narcotics consumption were the only two significant predictors among males (Table S2). For narcotics, ten males and eight females had positive scores. For all the variables included in both the wider and the final model, there were none statistically significant gender interaction terms (in both unadjusted and adjusted models – calculation not shown in any of the tables).

Discussion

In this study, the main finding was that baseline steps per day, substance use (alcohol and illicit drugs) and plasma growth hormone were independent predictors of physical activity six months after acute EBV infection, whereas variables reflecting immune or infectious disease processes had no or limited predictive power.

Steps per day at baseline was the most important predicting factor; the participants who were more active during acute illness were more active six months later. This finding may reflect habits; i.e., participants tend to keep up with their usual activities regardless of infectious episodes. Alternatively, physical activity might positively influence the recovery processes after

infectious mononucleosis, as suggested by some previous reports (16, 17, 19, 20, 27). Low physical activity during acute infection does not seem to be a measure for illness severity as variables reflecting symptom load, infectious and immune responses did not influence the final model.

Adjusting for baseline measurements of the dependent variable may cause interpretation challenges in observational studies (28). In the final model the estimates for substance use (alcohol/illicit drugs) and growth hormone did not change when baseline steps per day was removed from the final model. They also stayed the same in a model where change in steps per day was set as dependent variable.

Self-reported alcohol and narcotics/illicit drug consumption were also independent predictors in the final multiple linear regression model (Table 4). The association between alcohol consumption and physical activity was negative, in line with research on adults showing that high consumers are habitually less active than non- and moderate drinkers (29). Surprisingly, for narcotics/illicit drugs, the association in the present study was positive: Adolescents that used narcotics/illicit drugs tended to have a higher level of physical activity than the non-users. This result contrasts previous findings on sport participation among adolescents (30). A possible explanation might be that some of the participants in the present study use doping to promote sports achievements, or illicit stimulants; unfortunately, our data set does not allow us to pursue this hypothesis in the present study. Research on illicit drug use in Norway show that cannabis is the most prevalent illicit drug among adolescents (31). Baseline plasma growth hormone level was negatively associated with physical activity six months later. Growth hormone increases with different types of stress, such as physical activity as well as psychological challenges (32). Previous studies have shown that sedentary individuals have a higher growth hormone response to physical activity compared to fit individuals (33). In the present study, we speculate that those

being less active at six months are less fit at baseline, which in turn might be associated with a stronger growth hormone response to the psychological distress of undergoing an extensive investigational program (34).

Interestingly, the large number of variables related to baseline infectious of immune processes showed little or no association to physical activity six months later. Thus, reduced physical activity six months after acute EBV infection does not seem to be a direct consequence of the infection *per se,* nor the related immune response.

An earlier publication on the same cohort identified variables related to symptoms and functions, as the best predictors for fatigue six months after acute EBV infection (11). Interestingly, this study also shows a low predictive value of variables reflecting infectious and immune processes. Otherwise, the prediction model for physical activity was strikingly different to the predicting model for fatigue. In CFS clinical trials, steps per day has been used as a proxy for treatment monitoring i(14). The difference in prediction-models questions this practice.

Strengths and limitations

Strengths of the present study are the large sample size of adolescents with acute EBV infection, the low number of drop-outs and the wide assessment of each participant. Ideally, participants should also have been assessed prior to the acute EBV infection, but this was not practically feasible.

The number of variables measured and included in the analysis poses a challenge in the interpretation of the results. Basing variable selection on p-values tends to lead to overestimation of associations, and there is also a high risk of false positive findings. Our model should therefore be regarded as exploratory rather than confirmatory.

Another limitation is the missing activity data. A total of 27 (13.5%) participants had no valid activity measurements six months after the acute EBV infection. Our primary analysis is based on multiple imputation of missing values. The main weakness of this strategy is that data are assumed to be missing at random, which is an assumption that is difficult to verify. The sensitivity analysis using only actual measurements showed…. which is somewhat reassuring, even if a complete case analysis is expected to be biased.

Conclusion

Baseline physical activity (steps per day), substance use (alcohol and illicit drugs), and plasma growth hormone are independent predictors of physical activity 6 months after an acute EBV infection in adolescents, whereas markers of the infection and associated immune response have weak predictive power. The possible benefit of physical activity in the acute phase of EBV infection should be addressed in further studies.

List of abbreviations

CEBA - Chronic fatigue following acute EBV infection in adolescents

CFS - Chronic Faigue Syndrome

CRP - C-reactive protein

EBV - Epstein-Barr virus

IM - Infectious Mononucleosis

Declarations

Conflict of Interest

None of the authors have conflict of interest or financial relationships relevant to this article to disclose.

Founding

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Tables

Table 1. Serological patterns proving acute EBV infection

	EBV-VCA IgM	EBV-VCA IgG	EBNA IgG	Heterophile antibodies[1]
Pattern 1	Positive (⩾40 U/ml)	Negative (<20 U/ml)	Negative (<20 U/ml)	Positive
Pattern 2	Positive (⩾40 U/ml)	Positive (⩾20 U/ml)	Negative (<20 U/ml)	-

[1]The test for heterophile antibodies was only executed when the specific tests alone were inconclusive

Table 2. Number of activPAL registrations with days of valid recordings

	EBV patients	
Days of valid recordings	*Baseline*	*6 months*
7	161	143
6	8	7
5	9	8
4	3	5
3	2	5
2	2	5
All missing	15	27

Table 3. Cohort characteristics

	Patients at baseline (n=200)	Patients at six months (n=195)	p-value (baseline vs six months)[1]
Background			
Sex - no. males (%)	71 (35.5%)	n.a.	n.a.
Age, years - mean (SD)	16.9 (1.6)	17.4 (1.6)	<0.001
BMI, kg/m^2 - mean (SD)	21.3 (2.6)	22.2 (2.6)	<0.001
Symptoms and functional impairment			
Days since debut of symptoms, self reported - mean (SD)	30.2 (6.6)	n.a.	n.a.
Chalder Fatigue Questionnaire (CFQ), total score - mean (SD)[3]	19.5 (4.7)	15.2 (5.1)	<0.001
Infectious Symptoms, total score - mean (SD)	2.7 (0.9)	1.8 (0.7)	<0.001
Functional Disability Inventory, total score - mean (SD)	16.6 (11.8)	6.6 (8.8)	<0.001
Steps/day, number - mean (SD)	7515 (3080)	9046 (3438)	<0.001
Clinical findings			
Epstein-Barr Virus (EBV) load, copies in blood - no. (%)			0.111
Negative (<160)	49 (24.9%)	82 (43.6%)	
Low (1600 to 2000)	115 (58.4%)	61 (32.4%)	

Moderate/high (>2000)	33 (16.8%)	45 (23.9%)	
EBV Viral Capsid Antigen (VCA) IgM, titer - median (IQR)	160 (73)	20 (162)	<0.001
EBV-VCA-IgG, titer - median (IQR)	69 (67)	169 (162)	<0.001
EBV Nuclear Antigen (EBNA) IgG, titer - median (IQR)	0 (0)	98 (205)	<0.001
Serum total IgG, g/L - mean (SD)	12.0 (2.7)	9.9 (1.8)	<0.001
Blood Lymphocyte count, 10^9 cells/L - median (IQR)	2.3 (0.8)	1.9 (0.7)	<0.001
Serum Alanine Transaminase (ALT), IU/L - median (IQR)	33 (23)	24 (9)	<0.001

n.a.= not applicable. [1]Based on t-test, Mann-Whitney test or chi-square test, as appropriate. [2]Steps/day at 6 months is defined as the dependent variable for the prediction analyses, cf. Table 2 and 3.

Table 4. Baseline predictors of physical activity six months after acute EBV infection. Final multiple linear regression model

	Linear regression coefficient B (CI)	**p-value**	**Δadj.R^2 [3]**
Steps/day, number	0.4 (0.2 to 0.6)	p<0.001	0.122
Usage of alcoholic beverages[1]	-1757 (-2863 to -651)	0.002	0.052
Usage of narcotics/illicit drugs[1]	2100 (626 to 3574)	0.005	0.031
Serum Growth Hormone, µg/L	-148 (-266 to -29.5)	0.015	0.025
Explained variance (adjusted R^2) of model[5]	0.34		

Missing data was replaced by multiple imputation; a detailed explanation of the procedures for model generating is given in Pedersen et al 2018.1 Dichotomously scored (0=never, 1=occasionally or more often). 2Explained variance (adjusted R2) is calculated as the pooled average from 5 imputed dataset. 3The Δadj. R2-value indicates the change in explained variance (adjusted R2) of the entire model when one variable is removed from the model.

Table S1. All simple linear regression models between possible variables at baseline and physical activity (steps per day) six months after acute EBV infection

		original variables		imputed variables	
Background		**Linear regression coefficient B (CI)**	**p-value**	**Linear regression coefficient B (CI)**	**p-value**
Sex - no. males (%)	71 (35.5%)	-719 (-1797 to 359)	0.190		
Age at inclusion, years - mean (SD)	16.9 (1.6)	-212 (-536 to 113)	0.200		
BMI, kg/m^2 - mean (SD)	21.3 (2.6)	89.5 (-110 to 289)	0.376		
Days since debut of symptoms, self reported - mean (SD)	30.2 (6.6)	4.8 (-78.4 to 87.9)	0.910		
Ethnicity - no. (%)					
Scandinavian	184 (92.5%)		0.208		
Half Scandinavian	10 (5%)	-75.5 (-2288 to 2137)			
Not Scandinavian	5 (2.5%)	2769.0 (-313 to 5851)			
Lives with… - no. (%)					
…both parents	142 (71.4%)		0.239		
…divorced parents, alternating	17 (8.5%)	-1002 (-2856 to 852)			
…one parent	35 17.5%)	-666 (-2028 to 697)			
…alone	3 (1.5%)	3044 (-915 to 7003)			
…other	2 (1%)	-3772 (-10575 to 3031)			
Parents' highest education - no. (%)					
Primary school	1 (0.5%)		0.653		
Secondary school	47 (23.9%)	-3792 (-10733 to 3149)			
Lower university	97 (49.2%)	-3931 (-10827 to 2965)			
Higher university	52 (26.4%)	-3495 (-10428 to 3438)			
Siblings - no. (%)					
0	29 (14.5%)		0.580		
1	109 (54.5%)	-1002 (-2582 to 579)			
2	47 (47%)	-417 (-2207 to 1373)			
≥3	15 (7.5%)	-557 (-2817 to 1702)			
Usage of alcoholic beverages - no. (%)					
Never	69 (36.7%)	-1376 (-2468 to -2468)	0.014	-1348 (-2440 to -255)	0.016
Occationally	119 (63.3%)				

Usage of tobacco products - no. (%)					
Never	107 (56.9%)	-874 (-1949 to 208)	0.110		
Occationally	81 (43.1%)				
Usage of narcotics/illicit drugs - no. (%)					
Never	170 (90.4%)	1730 (40.6 to 3419)	0.045	1484 (-227 to 3195)	0.088
Occationally	18 (9.6%)				
Personality/life events					
Child and Adolescent Perfectionism Scale (CAPS), total score - mean (SD)	36.6 (10.15)	-18.4 (-71.1 to 34.4)	0.493		
CAPS Subscore: Self oriented striving - mean (SD)	10. 28 (2.80)	154 (-35.9 to 343)	0.111		
CAPS Subscore: Self oriented critical - mean (SD)	9.73 (3.65)	-60.0 (-207 to 86.7)	0.420		
CAPS Subscore: Socially perscribed - mean (SD)	16.6 (6.0)	-66.6 (-157 to 24.0)	0.149		
Life Event Checklist (LEC), total score of positive events last year - median (IQR)	7.0 (7.0)	14.9 (-429 to 459)	0.947		
LEC, total scor of all positive events - median (IQR)	7.0 (8.0)	15.4 (-408 to 439)	0.943		
LEC, total score of negative events last year- median (IQR)	5 (8)	-219 (-564 to 125)	0.211		
LEC, total score of all negative events - median (IQR)	7 (10)	-229 (-562 to 104)	0.176		
Clinical symptoms					
Chalder Fatigue Questionnaire (CFQ), total score	19.5 (4.71)	-117.3 (-231 to -3.1)	0.044	-95.1 (-209 to 18.2)	0.100
Post-exertional Malaise, single item - mean (SD)	1·5 (0·6)	-245 (-646 to 156)	0.230		
Infectious Symptoms, mean score - mean (SD)	2.7 (0.9)	-949 (-1557 to -341)	0.002	-825 (-1619 to -30.8)	0.043
Hypersensitivity Symptoms, mean score - mean (SD)	1.7 (1.0)	-520 (-1077 to 36.4)	0.067	-406 (-1072 to 261)	0.223
Brief Pain Inventory (BPI), total pain severity score - mean (SD)	10.9 (4.9)	-186 (-294 to 77.8)	0.001	-156 (-267 to -43.7)	0.007
BPI, average pain single item score - mean (SD)	2.7 (1.2)	-745 (-1179 to -311)	0.001	-622 (-1070 to 175)	0.007
Karolinska Sleep Questionnaire (KSQ), total score - mean (SD)	52.5 (12.4)	68.9 (25.6 to 112)	0.002	58.5 (12.5 to 104)	0.013
KSQ Subscore: Insomnia - mean (SD)	15.6 (4.8)	141 (32.0 to 250)	0.012	115 (-2.8 to 233)	0.056
KSQ Subscore: Awakenings - mean (SD)	10.2 (3.6)	157 (4.2 to 310)	0.044	131 (-33.9 to 296)	0.117
KSQ Subscore: Sleepy at daytime - mean (SD)	13.9 (4.2)	191 (65.6 to 316)	0.003	185 (42.7 to 327)	0.012
Clinical findings					
Tympanic temperatur, ºC - mean (SD)	36.3 (0.5)	-892 (-2002 to 219)	0.115		

Maximum spleen length, cm - mean (SD)	12.6 (1.7)	129 (-179 to 437)	0.411		
Pain Pressure Threshold finger nail, N/cm^2 - mean (SD)	10.5 (4.5)	14.1 (-96.9 to 125)	0.802		
Pain Pressure Threshold trapezius muscle, N/cm^2 - mean (SD)	5.4 (3.1)	27.6 (-136 to 191)	0.740		
Blood Haemoglobin concentration, g/dL - mean (SD)[2]	12.7 (1.2)	382 (-72.2 to 837)	0.099		
Blood Platelet count, 10^9 cells/L - mean (SD)	238 (58.3)	-5.1 (-14.2 to 4.1)	0.275		
Serum Alanine Transaminase (ALT), IU/L - median (IQR)	33.0 (23)	-0.7 (-13.2 to 11.9)	0.914		
Serum Gamma-Glutamyl Transpeptidase (GGT), IU/L- median (IQR)	27.0 (26)	-11.1 (-30.3 to 8.1)	0.255		
Serum Total Bilirubin, µmol/L- median (IQR)	10.0 (6)	-43.4 (-146 to 59.5)	0.406		
Plasma International Normalized Ratio (INR) - median (IQR)	1.1 (0.6)	1451 (-4295 to 7197)	0.619		
Serum Creatinine, µmol/L - mean (SD)	63.5 (10.0)	-21.8 (-72.9 to 29.3)	0.401		
Serum Creatinine Kinase (CK), IU/L - median (IQR)	53.0 (36)	1.7 (-3.4 to 6.7)	0.510		
Serum 25-OH-Vitamin D, nmol/L - mean (SD)	57.5 (20.9)	6.7 (-19.2 to 32.6)	0.609		
Serum Vitamin B_{12}, pmol/L - median (IQR)	320 (170)	2.1 (-2.0 to 6.1)	0.320		
Emotions					
Hospital Anxiety and Depression Scale (HADS), total score - mean (SD)	11.2 (5.8)	-113 (-203 to 24.0)	0.013	-97.2 (-182 to 12.3)	0.025
HADS Subscore: Anxiety - mean (SD)	6.4 (3.2)	-163 (-328 to 1.4)	0.052	-147 (-321 to 26.7)	0.096
HADS Subscore: Depression - mean (SD)	4.8 (3.6)	-183 (-334 to -32.1)	0.018	-139 (-282 to 2.7)	0.055
Toronto Alexithymia Scale-20 (TAS-20), total score - mean (SD)[1]	51.9 (10.8)	-32.4 (-82.9 to 18.0)	0.206	-35.3 (-94.8 to 24.2)	0.234
TAS-20 Subscore: Difficulty identifying feelings - mean (SD)	19.5 (6.9)	-71.7 (151 to 7.5)	0.076	-75.7 (-176 to 24.7)	0.132
TAS-20 Subscore: Difficulty describing feelings - mean (SD)[1]	21.4 (6.9)	-37.1 (-152 to 78.3)	0.527	-39.7 (-170 to 90.3)	0.539
TAS-20 Subscore: Externally oriented thinking - mean (SD)[1]	11.0 (2.7)	54.4 (-142 to 251)	0.585	42.3 (-197 to 281)	0.719
Penn State Worry Questionnaire, total score - mean (SD)	43.1 (12.5)	-39.9 (-81.5 to 1.7)	0.060	-38.3 (-79.8 to 3.2)	0.071
Brief Illness Perception Questionnaire, total score - mean (SD)	40.9 (10.8)	-14.6 (-64.0 to 34.8)	0.560		
Infection					
Epstein-Barr Virus (EBV) load, copies in blood - no. (%)			0.518		
Negative (<160)	49 (24.9)				
Low (1600 to 2000)	115 (58.4)	-512 (.1785 to 762)	0.429		
Moderate/high (>2000)	33 (16.8)	-972 (-2672 to 728)	0.261		
EBV virus load, copies in throat - no. (%)			0.695		

Negative	10 (5.2)				
Low (threshold cycle in PCR (CT), values >32)	26 (13.5)	77.1 (-2063 to 2217)	0.943		
Moderate (CT values 28 to 32)	128 (66.7)	635.8 (-1088 to 2359)	0.467		
High (CT values <28)	28 (14.6)	-158.8 (-2344 to 2027)	0.886		
EBV Viral Capsid Antigen (VCA) IgM, titer - median (IQR)	160 (73)	-2.7 (-13.5 to 8.1)	0.623		
EBV-VCA-IgG, titer - median (IQR)	69.00 (67)	-0.8 (-6.6 to 4.9)	0.775		
EBV Nuclear Antigen (EBNA) IgG, titer - median (IQR)	0.00 (0)	-3.0(-2331 to 2325)	0.998		
Cytomegalovirus (CMV) IgM, titer - median (IQR)	0.0 (0.0)	400 (-228 to 1028)	0.210		
CMV IgG, titer - median (IQR)	0.0 (323)	0.7 (-1.9 to 3.4)	0.608		
Borrelia burgdorferi IgM, titer - no. (%)			0.317		
Negative	99 (50)				
Reactive	61 (30.8)	-126 (-1324 to 1073)	0.836		
Greyzone	17 (8.6)	1551 (-396 to 3498)	0.118		
Positive	21 (10.6)	-623 (-2334 to 1089)	0.474		
B. burgdorferi IgG, titer - no. (%)			0.670		
Negative	191 (96.5)				
Greyzone	5 (2.5)	1537 (-1905 to 4978)	0.379		
Positive	2 (1)	420 (-4418 to 5258)	0.864		
Immunity					
Serum high sensitive CRP, mg/L - median (IQR)	0.40 (0.86)	56.7 (-153 to 266)	0.569		
Serum total IgG, g/L - mean (SD)	12.0 (2.7)	-217 (-405 to -27.8)	0.025	-189 (-402 to 24.5)	0.082
Serum total IgM, g/L - mean (SD)	1.5 (0.7)	-565 (-1296 to 166)	0.129		
Serum total IgA, g/L - mean (SD)	2.2 (0.9)	-267 (-828 to 294)	0.349		
Blood Leukocyte total count, 10^9 cells/L - median (IQR)	5.2 (1.7)	29.9 (-365 to 425)	0.881		
Blood Lymphocyte count, 10^9 cells/L - median (IQR)	2.3 (0.8)	-100 (-816 to 616)	0.783		
Blood Monocyte count, 10^9 cells/L - median (IQR)	0.5 (0.3)	-901 (-3627 to 1825)	0.515		
Blood Neutrophil count, 10^9 cells/L - median (IQR)	2.2 (1.2)	108 (-432 to 649)	0.693		
Blood Eosinophil count, 10^9 cells/L - median (IQR)	0.1 (0.1)	1588 (-1780 to 4955)	0.353		
Blood Basophil count, 10^9 cells/L - median (IQR)	0.0 (0.1)	-2979 (-14069 to 8112)	0.597		
Blood T cell ($CD3^+$) total count, 10^6 cells/L - median (IQR)	1793 (710)	-0.4 (-1.3 to 0.4)	0.330		

Blood T cell ($CD3^+$) fraction (of lymfocyte count), % - mean (SD)	81.3 (8.3)	-59.6 (-141 to 21.8)	0.150		
Blood double negative T cell ($CD4^-CD8^-$) subset (of $CD3^+$ count), % - median (IQR)	0.7 (0.5)	-71.7 (-1666 to 1522)	0.929		
Blood cytotoxic T cell ($CD8^+$) count, 10^6 cells/L- median (IQR)	842 (463)	-0.7 (-1.9 to 0.5)	0.267		
Blood cytotoxic T cell ($CD8^+$) fraction (of lymfocyte count), % - mean (SD)	40.5 (9.7)	-27.3 (-83.5 to 28.9)	0.339		
Blood early effector memory T cell subset (of $CD8^+$ count), % - mean (SD)	28.5 (10.5)	0.4 (-49.1 to 49.9)	0.988		
Blood late effector memory T cell subset (of $CD8^+$ count), % - median (IQR)	5.2 (5.8)	1.0 (-101 to 103)	0.985		
Blood helper T cell ($CD4^+$) count, 10^6 cells/L - median (IQR)	753 (274)	-0.8 (-2.9 to 1.3)	0.436		
Blood helper T cell ($CD4^+$) fraction (of lymfocyte count), % - mean (SD)	34.3 (7.9)	-1.3 (-68.1 to 65.5)	0.970		
Blood recent thymic emigrant T cell subset (of $CD4^+$ CD45RA+ T cell count), % - mean (SD)	69.0 (10.3)	27.9 (-21.6 to 77.4)	0.267		
Blood naïve T cell subset (of $CD4^+$ count), % - mean (SD)	61.4 (12.2)	7.9 (-34.5 to 50.3)	0.712		
Blood follicular T cell subset (of $CD4^+$ count), % - median (IQR)	6.4 (2.9)	-62.0 (-202 to 77.4)	0.381		
Blood regulatory T cell subset (of $CD4^+$ count), %- median (IQR)	5.3 (2.0)	184 (-150 to 518)	0.279		
Blood memory T cell subset (of $CD4^+$ count), % - mean (SD)	51.0 (11.4)	-14.3 (-61.2 to 32.6)	0.548		
Blood B cell ($CD19^+$) total count, 10^6 cells/L - median (IQR)	168 (109)	2.1 (-3.4 to 7.6)	0.454		
Blood B cell ($CD19^+$) fraction (of lymfocyte count), % - median (IQR)	7.4 (4.9)	59.8 (-12.8 to 132)	0.106		
Blood naïve B cell subset (of $CD19^+$ count), % - mean (SD)	81.4 (8.1)	15.3 (-49.2 to 79.9)	0.640		
Blood transitoric B cell subset (of $CD19^+$ count), % - median (IQR)	4.3 (4.7)	197 (44.1 to 350)	0.012	162 (16.1 to 307)	0.029
Blood class switch B cell subset (of $CD19^+$ count), % - median (IQR)	4.1 (4.0)	-48.3 (-193 to 96.3)	0.510		
Blood IgM memory B cell subset (of $CD19^+$ count), % - median (IQR)	8.1 (5.4)	-13.2 (-135 to 108)	0.830		
Blood plasmablast subset (of $CD19^+$ count), % - median (IQR)	0.3 (0.5)	-245 (-668 to 179)	0.256		
Blood $CD21^{low}$ B cell subset (of CD19+ count), % - median (IQR)	1.8 (1.8)	61.2 (-250 to 372)	0.698		
Blood NK cells ($CD16^+CD56^+CD3^-$) count, 10^6 cells/L - median (IQR)	192 (149)	1.5 (-1.8 to 4.8)	0.372		
NK cell function fraction (degranulated NK cells of total NK cell count), % - mean (SD)	26.6 (7.3)	36.5 (-37.4 to 110.4)	0.330		
Neuroendocrinology					
Plasma Norepinephrine, pmol/L - mean (SD)	1533 (693)	-0.1 (-1.1 to 0.9)	0.848		
Urine Norepinephrine:Creatinine ratio, nmol/mmol - median (IQR)	0.0104 (0.01)	-12757 (-112236 to 86722)	0.800		
Plasma Epinephrine, pmol/L - median (IQR)	360 (238)	-0.8 (-2.8 to 1.2)	0.441		
Urine Epinephrine:Creatinine ratio, nmol/mmol - median (IQR)	0.0017 (0.0)	-30251.5 (-434978.0 to 374475.0)	0.883		
Plasma Adrenocorticotropic Hormone (ACTH), pmol/L - median (IQR)	4.3 (3.2)	-51.4 (-224 to 122)	0.558		

Serum Cortisol, nmol/L - median (IQR)	335 (190)	-1.8 (-5.5 to 1.9)	0.331		
Urine Cortisol:Creatinine ratio, nmol/mmol - median (IQR)					
Serum Thyroid Stimulating Hormone (TSH), mIE/L - median (IQR)	2.1 (1.3)	-195 (-666 to 276)	0.415		
Serum free Thyroxine, pmol/L - median (IQR)	11.0 (2)	132 (-434 to 171)	0.391		
Serum Growth Hormone, µg/L - median (IQR)	0.9 (4.8)	-133 (-257 to -9.5)	0.035	-135 (-269 to -2.3)	0.046
Serum Insulin-like Growth Factor (IGF-1), nmol/L - median (IQR)	49.3 (21.5)	30.1 (0.3 to 59.8)	0.048	30.0 (-4.8 to 64.8)	0.090
Serum Prolactine, mIU/L - median (IQR)	200 (100)	-1.7 (-8.5 to 5.1)	0.623		
Cognition		B (CI)	sig.		
Digit Span Forward, total sum score - mean (SD)	9.0 (1.9)	-1.7 (-274 to 270)	0.990		
Digit Span Backward, total sum score - mean (SD)	6.2 (1.9)	18.7 (-250 to 288)	0.891		
Hopskin s Verbal Learning Test-Revised (HVLT-R) Learning/Immediate Recall, total sum score - mean (SD)	28.1 (4.0)	53.6 (-75.1 to 182)	0.412		
HVLT-R Delayed Recall, total sum score - mean (SD)	9.9 (1.8)	50.2 (-242 to 343)	0.735		
HVLT-R Correct Recognition		581 (-719 to 1880)	0.379		
All correct - no. (%)	162 (81)				
Less than all correct - no. (%)	38 (19)				
HVLT-R False Recognition		177 (-1111 to 1465)	0.787		
No false recognition - no. (%)	158 (79)				
One or more false recognition - no. (%)	42 (21)				
Color-Word Interference (CWI) condition 1, T-score - median (IQR)	31 (7)	-1.9 (-88.9 to 85.0)	0.965		
CWI condition 2, T-score - median (IQR)	23 (6)	-16.7 (-134 to 100)	0.779		
CWI condition 3, T-score - median (IQR)	51.5 (16)	7.6 (-33.6 to 48.8)	0.716		
CWI condition 3, no. of errors - median (IQR)	2 (2)	-99.3 (-357 to 158)	0.447		
CWI condition 4, T-score - median (IQR)	57 (16)	3.3 (-39.1 to 45.7)	0.878		
CWI condition 4, no. of errors - median (IQR)	2 (3)	-90.9 (-362 to 181)	0.510		
Wechsler Abbrivated Scale of Intelligence, 4th edition (WASI-IV) Materix resoning, T-scores	27.7 (4.6)	7.1 (-103 to 118)	0.899		
WASI-IV Vocabulary, T-scores - mean (SD)	59.8 (7.5)	31.1 (-37.0 to 99.3)	0.368		
Estimated Full-Scale Intelligence Quotient (IQ) - mean (SD)					
Autonomic cardiovascular control					

Heart Rate (HR) supine, beats/min - mean (SD)	65.1 (9.3)	-98.4 (-154 to -42.6)	0.001	-83.6 (-141.2 to -26.1)	0.005
Systolic Blood Pressure (SBP) supine, mmHg - mean (SD)	98.9 (8.6)	41.8 (-16.7 to 100)	0.160		
Diastolic Blood Pressure (DBP) supine, mmHg - mean (SD)	59.5 (6.7)	19.9 (-56.7 to 96.4)	0.609		
Total Periferal Resistance Index (TPRI) supine, mmHg/L/min/m^2 - mean (SD)	12.7 (2.2)	52.5 (-281 to 386)	0.756		
High Frequency Variability of the RR-interval (HF-RRI) supine, ms^2 - median (IQR)	1054 (1703)	0.1 (-0.1 to 0.3)	0.311		
Low Frequency Variability of the RR-interval (LF-RRI) supine, ms^2 - median (IQR)	663 (910)	0.3 (-0.1 to 0.8)	0.173		
LF-RRI:HF-RRI ratio supine - median (IQR)	0.63 (0.56)	197 (-840 to 1234)	0.708		
Low Frequency Variability of Diastolic Blood Pressure (LF-DBP) supine, $mmHg^2$ - median (IQR)	3.0 (3.0)	26.0 (-105 to 157)	0.696		
HR response to Controlled Breathing (CB), beats/min - mean (SD)	0.95 (2.8)	-96.1 (-280 to 88.0)	0.304		
SBP response to CB, mmHg - mean (SD)	0.12 (5.6)	-71.8 (-165 to 21.6)	0.131		
DBP response to CB, mmHg - mean (SD)	-3.38 (4.76)	-79.6 (-188 to 29.1)	0.150		
TPRI response to CB, mmHg/L/min/m^2 - mean (SD)	-0.18 (0.61)	-577 (-1427 to 273)	0.182		
HF-RRI response to CB, ms^2 - median (IQR)	101 (1294)	-0.3 (-0.9 to 0.3)	0.328		
LF-RRI response to CB, ms^2 - mean (SD)	-333 (431)	0.1 (-0.3 to 0.5)	0.762		
LF-RRI:HF-RRI ratio response to CB - mean (SD)	-0.21 (0.56)	-354 (-1495 to 787)	0.541		
LF-DBP response to CB, $mmHg^2$ - mean (SD)	-0.75 (1.91)	-11.5 (-279 to 257)	0.933		
HR response to Orthostatic Challenge (OC), beats/min - mean (SD)	30.1 (11.6)	31.7 (-13.3 to 76.6)	0.166		
SBP response to OC, mmHg - mean (SD)	-1.48 (10.4)	-8.2 (-58.9 to 42.5)	0.750		
DBP response to OC, mmHg - mean (SD)	7.18 (8.99)	10.7 (-47.5 to 69.0)	0.716		
TPRI response to OC, mmHg/L/min/m^2 - mean (SD)	0.83 (1.58)	9.8 (-324 to 344)	0.954		
HF-RRI response to OC, ms^2 - median (IQR)	-1369 (2237)	-0.1 (-0.4 to 0.1)	0.274		
LF-RRI response to OC, ms^2 - mean (SD)	-98.2 (1652)	-0.1 (-0.4 to 0.2)	0.453		
LF-RRI:HF-RRI ratio response to OC - mean (SD)	1.91 (1.69)	50.4 (-264 to 365)	0.752		
LF-DBP response to OC, $mmHg^2$ - mean (SD)	-0.51 (2.50)	-33.9 (-246 to 178)	0.753		
Function					
Functional Disability Inventory, total score - mean (SD)	16.6 (11.8)	-69.0 (-113 to -24.7)	0.002	-59.1 (-106 to -12.8)	0.013
Pediatric Quality of Life (PedsQL), total score - mean (SD)	66.5 (17.4)	50.8 (21.0 to 80.7)	0.001	45.1 (15.1 to 75.1)	0.003
Steps/day, number - mean (SD)	7515 (3080)	0.4 (0.3 to 0.6)	<0.001	0.4 (0.2 to 0.6)	<0.001

n.a.=not applicable. [1]Subscales in which total score or other subscales in the same questionnaire were significant, were imputed despite a insignificant bivariate linear regression finding. [2] Variables in which gender acted as a confounder were not included in the multiple imputation. A total of 306 statistical tests are desplayed in this table; a Bonferroni-correction for test multiplicity suggests a level of signifance at 0,05/188 = 0,0003.

Table S2. Baseline predictors of physical activity six months after acute EBV infection. Multiple linear regression models addressing the effect of sex differences.

	Multiple linear model including sex (n=200)		**Multiple linear model in female subgroup (n=129)**		**Multiple linear model in male subgroup (n=71)**		**Multiple linear model based on wide inclusion of variables**		
	B (CI)	p-value	B (CI)	p-value	B (CI)	p-value	B (CI)	p-value	Δadj.R^2 [5]
Steps/day, number	0.4 (0.2 to 0.6)	<0.001	0.5 (0.3 to 0.6)	<0.001	0.3 (-0.0 to 0.6)	0.055	0.31 (0.13 to 0.49)	0.001	0.062
Usage of alcoholic beverages[1]	-1752 (-2856 to -648)	0.002	-1440 (-2790 to -89.9)	0.037	-2336 (-4220 to -452)	0.015	-1472 (-2632 to -313)	0.014	0.035
Usage of narcotics/illicit drugs[2]	2075 (563 to 3586)	0.007	1457 (-712 to 3626)	0.185	2803 (365 to 5242)	0.024	2430 (978 to 3883)	0.001	0.041
Serum Growth Hormone, µg/L	-140 (-267 to -13.8)	0.030	-121 (-247 to 5.0)	0.060	-170 (-649 to 310)	0.486	-105 (-222 to 11.8)	0.078	0.010
Sex	1144 (-1283 to 996)	0.804							
Sleepy at daytime[3]							107 (-52.9 to 267)	0.179	0.011
Heart Rate (HR) supine, beats/min							-49.6 (-106 to 6.72)	0.084	0.011
Toronto Alexithymia Scale-20 (TAS-20), total score							-25.8 (-125 to 73.0)	0.570	0.005
TAS-20 Subscore: Externally oriented thinking							155 (-138 to 448)	0.279	0.009
Serum total IgG, g/ - mean (SD)							-131 (-320 to 57.3)	0.169	0.007
Explained varience (adjusted R^2) of model[4]	0.201		0.231		0.119		0.240		

All models are based on imputed datasets.[1] Occasionally or more often use of alcohol was scored as 1. [2] Ocasionally or more often use of illicit drugs was scored as 1. [3] Subscale from Karolinska Sleep Questionnare. [4]Explained variance (adjusted R^2) was calculated as the pooled average from 5 imputed dataset. [5]The Δadj. R2-value indicates the change in explained variance (adjusted R2) of the entire model when the variable is removed from the model.