ACTA PÆDIATRICA
NURTURING THE CHILD

Check for updates

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Lifestyle factors during acute Epstein–Barr virus infection in adolescents predict physical activity six months later

Maria Pedersen (marpeders@gmail.com)[1], Tarjei Tørre Asprusten[2], Kristin Godang[3], Truls Michael Leegaard[2,4], Liv Toril Osnes[5], Eva Skovlund[6], Trygve Tjade[7], Merete Glenne Øie[8,9], Vegard Bruun Bratholm Wyller[2,10]

1.Department of Pediatrics, Vestre Viken Hospital Trust, Drammen, Norway
2.Institute of Clinical Medicine, University of Oslo, Oslo, Norway
3.Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital, Oslo, Norway
4.Department of Microbiology and Infectional Control, Akershus University Hospital, Lørenskog, Norway
5.Department of Immunology, Oslo University Hospital, Oslo, Norway
6.Norwegian Institute of Public Health, Oslo, Norway
7.Fürst Medical Laboratory, Lørenskog, Norway
8.Department of Psychology, University of Oslo, Oslo, Norway
9.Research Division, Innlandet Hospital Trust, Lillehammer, Norway
10.Department of Pediatrics, Akershus University Hospital, Lørenskog, Norway

Keywords
Adolescents, Chronic fatigue, Epstein–Barr virus infection, Physical activity

Correspondence
M Pedersen, Department of Pediatrics, Vestre Viken Hospital Trust, N-3004 Drammen, Norway.
Tel: +47 95 77 11 70 |
Email: marpeders@gmail.com

Received
5 October 2018; revised 27 December 2018; accepted 22 January 2019.

DOI:10.1111/apa.14728

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. In this exploratory study, 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: Baseline physical activity, substance use and plasma growth hormone are independent predictors of physical activity six months after an acute EBV infection in adolescents, whereas markers of the infection and associated immune response do not seem to be associated with physical activity six months later.

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) characterised by fever, pharyngitis, swollen lymph nodes and malaise (2). In the adult population, more than 90% are EBV seropositive.

Infectious mononucleosis is often complicated by prolonged fatigue, and as many as 12–13% of EBV-infected individuals fulfil case definition of chronic fatigue syndrome (CFS) six months after the acute infection (3,4). 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 (5–9). However, in a recent study, virus load and other infectious markers had no predictive power (9).

Earlier studies suggest that CFS patients have lower activity levels compared to healthy controls (10–12). Graded exercise is an integrated part of some therapy protocols for CFS (13), and physical activity may modulate illness experiences (14) and increase general well-being (15). Furthermore, physical activity impacts markedly on immune processes and might influence underlying disease processes involving the immune system (16). Accordingly,

Abbreviations

CEBA, Chronic fatigue following acute EBV infection in adolescents; CFS, Chronic fatigue syndrome; CRP, C-reactive protein; EBV, Epstein-Barr virus; IM, Infectious mononucleosis.

Key notes

- Lifestyle factors are the main predictors for physical activity six months following acute Epstein–Barr virus (EBV) infection.
- The intensity or quality of infectious- and immune processes does not seem to predict.
- Physical activity during acute EBV infection is associated with physical activity six months later.

physical activity monitoring has been used as primary endpoint in CFS clinical trials (12).

Still, the relationship between physical activity and chronic fatigue remains to be fully characterised. 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 programmes, 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 hypothesised 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 EBV 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 (9). 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 (9): (i) A serological pattern indicating acute EBV infection (Table 1); (ii) Age between 12 and 20 years; and (iii) Living in one of the Norwegian counties Oslo, Akershus or Buskerud. Exclusion criteria were (i) More than six weeks since debut of symptoms suggesting acute EBV infection; (ii) Any chronic disease that needed regular use of medication; and (iii) Pregnancy.

Table 1 Serological patterns proving acute EBV infection

	EBV-VCA IgM	EBV-VCA IgG	EBNA IgG	Heterophile antibodies*
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)	–

*The test for heterophile antibodies was only executed when the specific tests alone were inconclusive.

Investigational programme

Participants were summoned to a one-day investigational programme at the CEBA study centre, Akershus University Hospital, Norway. Encounters were scheduled as soon as possible after debut of symptoms (baseline), with a follow-up visit six 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 anaesthetic ointment (EMLA®; AstraZeneca, Cambridge, UK) on both antecubital areas one hour before arriving.

The investigational programme 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 (9). 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 (i) supine rest; (ii) supine rest with controlled breathing; and (iii) 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, UT, 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 (17,18), and demographic and lifestyle background variables.

Activity monitoring

Activity monitoring was initiated immediately after the in-hospital investigational programme. All participants wore the activPAL™ accelerometer device (PAL Technologies, Glasgow, UK) for seven consecutive days. The activPAL™ was attached on the anterior midline on the participants thigh with custom made, waterproof adhesive tape. The participants were instructed to wear the activPAL™ at all times, and only take it off when the recording period was finished. The activPAL™ provides reliable data on both steps and position (19,20), and is validated for adolescents (21).

Data from the recording units were 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 behaviour 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 (22). 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 standard deviations 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 (9). 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 screening 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 re-entered one-by-one in the final model. The final model was constructed on pooled data from the five imputed datasets. A more detailed explanation of a similar model construction is reported elsewhere (9).

Table 2 Number of activPAL registrations with days of valid recordings

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

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).

Table 3 Cohort characteristics

	Patients at baseline (n = 200)	Patients at six months (n = 195)	p-value (baseline vs. six months)*
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)†	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. (%)			
Negative (<160)	49 (24.9%)	82 (43.6%)	0.111
Low (1600–2000)	115 (58.4%)	61 (32.4%)	
Moderate/high (>2000)	33 (16.8%)	45 (23.9%)	
EBV Viral Capsid Antigen (VCA) IgM, titre – median (IQR)	160 (73)	20 (162)	<0.001
EBV-VCA-IgG, titre - median (IQR)	69 (67)	169 (162)	<0.001
EBV Nuclear Antigen (EBNA) IgG, titre – 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.

*Based on *t*-test, Mann–Whitney test or chi-square test, as appropriate.

†Steps/day at six months is defined as the dependent variable for the prediction analyses, cf. Tables 2 and 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 six months, whereas baseline alcohol consumption and serum growth hormone levels were negatively associated (Table 4). The adjusted R^2 for the final model was 0.20. For narcotics, ten males and eight females had positive scores. For all the variables included in the final model, no statistically significant gender interactions were detected (both unadjusted and adjusted models, results not shown).

Sensitivity analyses using only actual measurements showed similar estimates of the regression coefficients, p-values and adjusted R^2 for the four variables (Table S2).

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; that is participants tend to keep up with their usual activities regardless of infectious episodes. Alternatively, physical activity might positively influence the recovery processes after IM, as suggested by some previous reports (14,16,23). 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 (24). 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 (25). 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 (26). 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 shows that cannabis is the most prevalent illicit drug among adolescents (27). 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 (28). Previous studies have shown that sedentary individuals have a higher growth hormone response to physical activity compared to fit individuals (29). 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 programme (30).

Interestingly, the large number of variables related to baseline infectious or 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 (9). Interestingly, this study also shows a general scarcity in the predictive value of variables reflecting infectious and immune processes. Otherwise, the prediction model for physical activity was strikingly different to the model for fatigue. In CFS clinical trials, steps per day has been used as

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.$R^{2\dagger}$
Steps/day, number	0.4 (0.2–0.6)	<0.001	0.122
Usage of alcoholic beverages*	−1757 (−2863 to −651)	0.002	0.052
Usage of narcotics/illicit drugs*	2100 (626–3574)	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‡	0.20		

Missing data was replaced by multiple imputation; a detailed explanation of the procedures for model generating is given in Pedersen et al. 2018.
*Dichotomously scored (0 = never, 1 = occasionally or more often).
†Explained variance (adjusted R^2) is calculated as the pooled average from five imputed dataset.
‡The Δadj. R^2-value indicates the change in explained variance (adjusted R^2) of the entire model when one variable is removed from the model.

a proxy for treatment monitoring (12). The difference between prediction-models questions this practice.

Despite assessing 149 possible predictors, the adjusted R-square of the final model is not higher than 20%. This shows that the variance of physical activity to a large extent is explained by factors beyond the scope of this study.

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 similar linear regression coefficients, p-values and effect sizes for the four variables in the final model (Table S2).

CONCLUSION

Baseline physical activity (steps per day), substance use (alcohol and illicit drugs), and plasma growth hormone are independent predictors of physical activity six 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.

CONFLICT OF INTEREST

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

FUNDING

This study was funded by the Health South–East Hospital Trust, Norway.

References

1. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964; 1: 702–3.
2. Balfour HH Jr, Odumade OA, Schmeling DO, Mullan BD, Ed JA, Knight JA, et al. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students. *J Infect Dis* 2013; 207: 80–8.
3. Katz BZ, Shiraishi Y, Mears CJ, Binns HJ, Taylor R. Chronic fatigue syndrome after infectious mononucleosis in adolescents. *Pediatrics* 2009; 124: 189–93.
4. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006; 333: 575.
5. Buchwald DS, Rea TD, Katon WJ, Russo JE, Ashley RL. Acute infectious mononucleosis: characteristics of patients who report failure to recover. *Am J Med* 2000; 109: 531–7.
6. Candy B, Chalder T, Cleare AJ, Peakman A, Skowera A, Wessely S, et al. Predictors of fatigue following the onset of infectious mononucleosis. *Psychol Med* 2003; 33: 847–55.
7. Petersen I, Thomas JM, Hamilton WT, White PD. Risk and predictors of fatigue after infectious mononucleosis in a large primary-care cohort. *QJM* 2006; 99: 49–55.
8. Chretien JH, Esswein JG, Holland WG, McCauley CE. Predictors of the duration of infectious mononucleosis. *South Med J* 1977; 70: 437–9.
9. Pedersen M, Asprusten TT, Godang K, Leegaard TM, Osnes LT, Skovlund E, et al. Predictors of chronic fatigue in adolescents six months after acute Epstein-Barr virus infection: a prospective cohort study. *Brain Behav Immun* 2018; 75: 94–100.
10. Evering RM, Tonis TM, Vollenbroek-Hutten MM. Deviations in daily physical activity patterns in patients with the chronic fatigue syndrome: a case control study. *J Psychosom Res* 2011; 71: 129–35.
11. Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, et al. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. *Arch Phys Med Rehabil* 2011; 92: 1820–6.
12. Sulheim D, Fagermoen E, Winger A, Andersen AM, Godang K, Muller F, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatr* 2014; 168: 351–60.
13. National Institute for Health and Care Excellence. Clinical guideline CG53. Chronic fatigue/myalgic enc3phalomyelitis (or enc3phalopaty): diagnosis and management, 2007.
14. Brown JD, Siegel JM. Exercise as a buffer of life stress: a prospective study of adolescent health. *Health Psychol* 1988; 7: 341–53.
15. Gauvin L, Spence JC. Physical activity and psychological well-being: knowledge base, current issues, and caveats. *Nutr Rev* 1996; 54: S53–65.
16. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 2000; 80: 1055–81.
17. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; 121: 953–9.
18. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, et al. Myalgic encephalomyelitis/chronic fatigue syndrome. *J CFS* 2003; 11: 7–115.
19. Grant PM, Ryan CG, Tigbe WW, Granat MH. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. *Br J Sports Med* 2006; 40: 992–7.
20. Ryan CG, Grant PM, Tigbe WW, Granat MH. The validity and reliability of a novel activity monitor as a measure of walking. *Br J Sports Med* 2006; 40: 779–84.

21. Dowd KP, Harrington DM, Donnelly AE. Criterion and concurrent validity of the activPAL professional physical activity monitor in adolescent females. *PLoS One* 2012; 7: e47633.
22. Wyller VB. Statistical analysis plan – CEBA, 2014.
23. Dalrymple W. Infectious mononucleosis. *Postgrad Med* 1964; 35: 345–9.
24. Lord FM. A paradox in the interpretation of group comparisons. *Psychol Bull* 1967; 68: 304–5.
25. Liangpunsakul S, Crabb DW, Qi R. Relationship among alcohol intake, body fat, and physical activity: a population-based study. *Ann Epidemiol* 2010; 20: 670–5.
26. Kwan M, Bobko S, Faulkner G, Donnelly P, Cairney J. Sport participation and alcohol and illicit drug use in adolescents and young adults: a systematic review of longitudinal studies. *Addict Behav* 2014; 39: 497–506.
27. SIRUS Norwegian Institute for Alcohol and Drug Research. The Drug Situation in Norway 2014. Annual report to the European Monitoring Centre for Drugs and Drug Addiction - EMCODA. Oslo, 2015.
28. Greenwood F, Landon J. Growth hormone secretion in response to stress in man. *Nature* 1966; 210: 540.
29. Bloom SR, Johnson RH, Park DM, Rennie MJ, Sulaiman WR. Differences in the metabolic and hormonal response to exercise between racing cyclists and untrained individuals. *J Physiol* 1976; 258: 1–18.
30. Jacobs HS, Nabarro JD. Plasma 11-hydroxycorticosteroid and growth hormone levels in acute medical illnesses. *Br Med J* 1969; 2: 595–8.

SUPPORTING INFORMATION

Additional Supporting Information may be found in online in the Supporting Information section at the end of the article:

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

Table S2 Sensitivity analyses - final multiple linear regression model with multiple imputed (MI) data and per protocol data (original dataset) for comparison.